06-24-10

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Docket No.: 64921.8011US
(PATENT)

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

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|---|---|
| Patentee: | Danek et al. |
| Application No.: | 09/296,040 |
| Filed: | April 21, 1999 |
| Patent No.: | 6,411,852 |
| Issued: | June 25, 2002 |

For: MODIFICATION OF AIRWAYS BY APPLICATION OF ENERGY

**APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. §1.56**

Assistant Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

06/24/2010 SDENBOB3 00000049 09296040
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Sir:

Applicant hereby files this application for extension of the patent term of U.S. Patent No. 6,411,852 under 35 U.S.C. §1.56 and 37 C.F.R. §1.710 *et seq.* The following information is submitted in accordance with 37 C.F.R. §1.740(a).

**1. 37 C.F.R. §1.740(a)(1)**

Identification of the Approved Product and Methods of Using the Approved Product

The Alair® Bronchial Thermoplasty System ("Alair System") is indicated for the treatment of severe persistent asthma in patients 18 years and older whose asthma is not well controlled with inhaled corticosteroids and long acting beta agonists as described in the Approval Order attached as Appendix A regarding Premarket Approval Application (PMA) No. P080032. The Alair System includes an Alair Catheter Model ATS 2-5 ("Catheter"), an Alair RF Controller Model ATS 200 ("Controller"), which includes a foot switch to operate the Controller, and a commercially available return electrode purchased

by the user, as shown in Figure 1 of the FDA Executive Summary regarding PMA No. P080032 (FDA Executive Summary) reproduced below and attached as Appendix H.

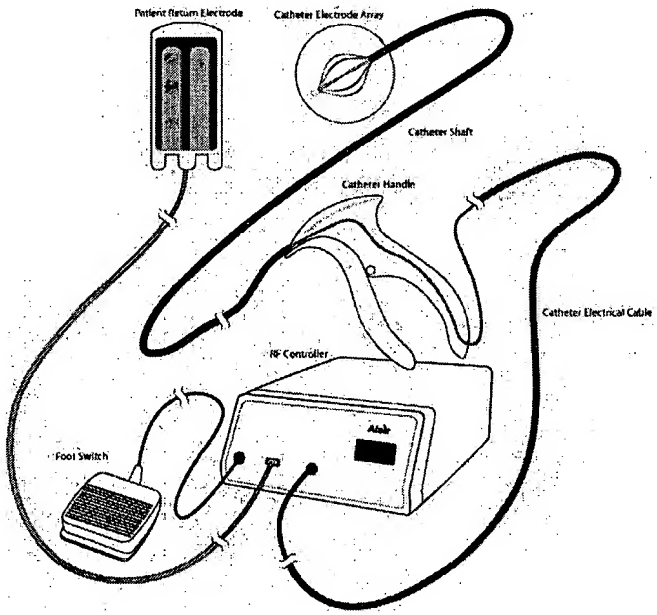



Figure 1: Schematic of The Alair System

The Catheter delivers RF energy from the Controller to desired target sites along the airways of a lung. The Catheter also senses the temperature of the airway and relays temperature feedback data to the Controller. The Controller generates low-power, temperature-controlled RF energy to achieve a predetermined temperature setting for a predetermined time period. The temperature set point, power limit, maximum energy delivery, and delivery time cannot be adjusted by the operator, but rather these parameters are configured in controller software algorithms that limit the maximum tissue temperature to 65°C over a maximum of 10 seconds with a total energy delivery not to exceed 120 Joules at each target site along an airway.

The Alair System treatment is an out-patient procedure that includes positioning a flexible bronchoscope at a target site in the lung of a patient and advancing the Alair Catheter through the bronchoscope until the distal tip of the catheter shaft is in

bronchoscopic view. When the electrode array of the Catheter is at the targeted site, the operator partially expands the electrode array so that the electrodes are close to or just touching the tissue at the targeted site. The axial position of the electrodes along the airway is adjusted to position the active electrodes as desired. The operator then further expands the electrode array until all four electrodes firmly contact the airway wall as shown in Figure 11 of the Catheter Instructions For Use ("Catheter IFU") attached as Appendix B.

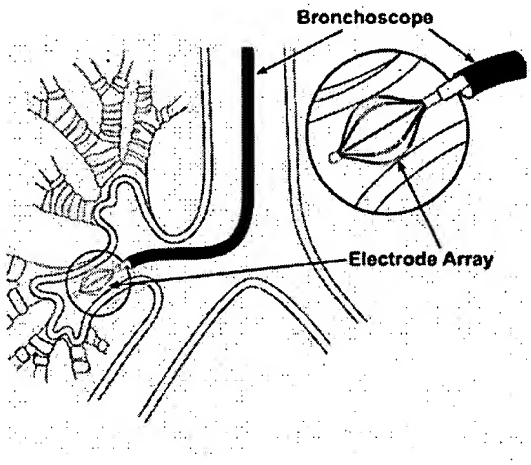



**Figure 11: Alair® Catheter in the Airway**

RF energy is then delivered to the targeted region by pressing and releasing the foot switch.

Complete treatment of any given airway requires delivering RF energy at a number of sites along the accessible length of the airway. The Catheter, therefore, must be repositioned and the electrode redeployed several times throughout a treatment. Referring to Figure 12 of the Catheter IFU reproduced below, the Catheter is initially placed distally in an airway, the electrode array is expanded, and the Controller is activated to deliver RF energy to one of the target sites along the airway.

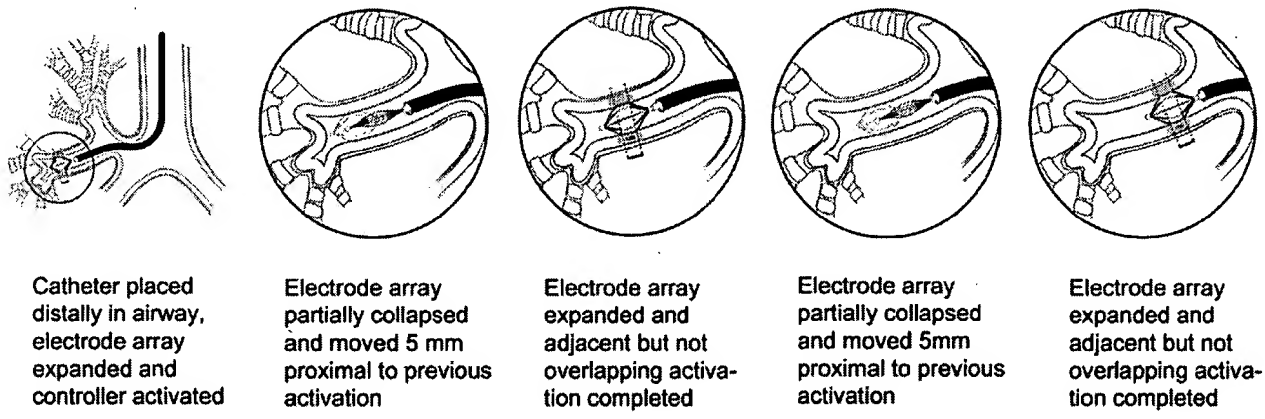
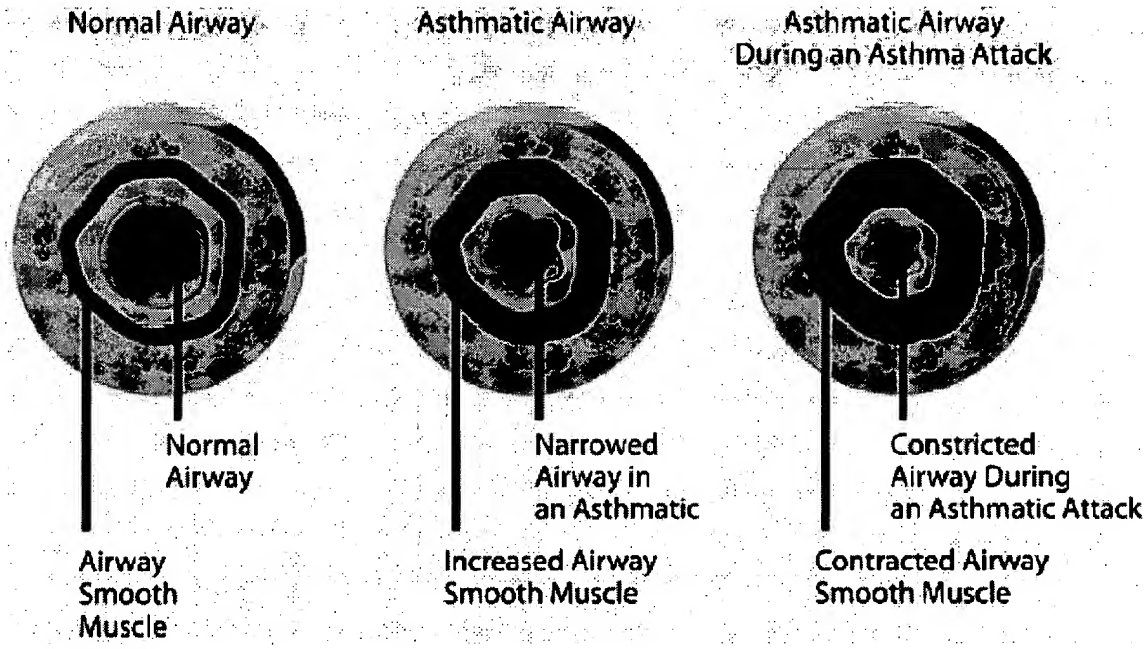



**Figure 12: Contiguous Placement and Activation**

After completing the initial target site, the electrode array is partially collapsed and moved proximally by 5 mm. The electrode array is then expanded and reactivated to deliver RF energy to the proximal location. These steps are repeated at approximately 5 mm increments to provide a contiguous placement of the electrodes along the length of the airway. This process delivers energy to the airway wall in a pattern having four lines that extend longitudinally along at least a portion of the airway.

The Alair System treatment has been shown in preclinical studies to reduce airway responsiveness and the ability to achieve pathological broncho-constriction by, at least in part, reducing the airway smooth muscle (ASM) within the airway walls of the lung. Contraction of the ASM is a main cause of airway constriction that leads to difficulty in breathing during asthma attacks. Severe asthma patients experience an increase in the

mass of ASM. This increase of ASM mass, together with inflammation of the airways, thickens airway walls and concomitantly decreases the inside diameter of the airways when the ASM contracts (i.e., shortens). The resulting decrease in airway diameter increases the resistance to airflow and further contributes to difficulty in breathing during asthma attacks. Figure 5 of the PMA Module 070003 Executive Summary (Appendix I), reproduced below, depicts a cross-sectional representation of (a) a normal airway, (b) an asthmatic airway, and (c) an asthmatic airway during an asthma attack.




The thermal energy delivered by the Alair System to the airway wall heats the tissue in a controlled manner intended to reduce, debulk, or partially eliminate ASM. Preclinical studies showed that the reduction of ASM (a) decreases the ability of airways to constrict/contract, (b) reduces resistance to airflow, (c) reduces responsiveness of the

airway, and (d) increases the resting diameter of the airway. (Danek et al. 2004[1], Brown et al. 2005[2].)

**2. 37 C.F.R. §1.740(a)(2)**

Identification of the Federal Statute Under Which the Regulatory Review Occurred

The regulatory review of the Alair System occurred under Section 515 of the Federal Food, Drug and Cosmetic Act. The pertinent regulations are set forth at 21 C.F.R. § 800 et seq.[3]

**3. 37 C.F.R. §1.740(a)(3)**

Identification of the Date on Which the Alair System Received Permission for Commercial Marketing

The Alair System was approved for commercial marketing on April 27, 2010, as set forth in the Approval Order in Appendix A.

**4. 37 C.F.R. §1.740(a)(4)**

Identification of Active Ingredient of Drug Product

Not applicable.

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[1] Danek CJ, Lombard CM, Dungworth DL, Cox PG, Miller JD, Biggs MJ, Keast TM, Loomas BE, Wizeman WJ, Hogg JC, Leff AR. Reduction in Airway Hyperresponsiveness to Methacholine by the Application of RF Energy in Dogs. J Appl Physiol. 2004, 97(5):1946-53.

[2] Brown RH, Wizeman W, Danek C, Mitzner W. Effect of Bronchial Thermoplasty on Airway Distensibility. Eur Respir J. 2005 Aug:26(2):277-82.

[3] 510(k) Application Nos. K980046 and K993900 were cleared in 1998 and 2000, respectively. Application No. K980046 was for the Bronchus Bronchial Catheter System having a balloon RF electrode array intended for foreign body removal and bronchial hemostasis. Application No. K993900 was for the Bronchus Coagulation Electrode System having a basket RF electrode array intended for coagulation or hemostasis in the tracheobronchial tree. Asthmatx, Inc. acquired 510(k) Application Nos. K980046 and K993900 via an assignment.

**5. 37 C.F.R. §1.740(a)(5)**

Statement of Timely Filing of Application

Under 37 C.F.R. §1.720(f), this application is being submitted within 60 days of the date that the Alair System was approved for commercial marketing. The last day on which this application can be submitted is June 25, 2010.

**6. 37 C.F.R. §1.740(a)(6)**

Identification of Patent

The present application seeks to extend the term of U.S. Patent No. 6,411,852, filed on April 21, 1999, which issued on June 25, 2002, and is currently set to expire on April 7, 2017 (the "'852 Patent"). The inventors are Dr. Michael D. Laufer, Christopher J. Danek, Thomas M. Keast, and Bryan E. Loomas.

**7. 37 C.F.R. §1.740(a)(7)**

Patent Copy

A copy of the '852 Patent, including the entire specification, claims and drawings, is attached as Appendix C.

**8. 37 C.F.R. §1.740(a)(8)**

Copy of Disclaimers, Corrections, Reexamination Certificates, and Maintenance Fee Payment Receipts

No disclaimer of any portion of the term of the '852 Patent has been made. A first Certificate of Correction dated May 13, 2003 (attached as Appendix D) corrected the listing of inventors to include Dr. Michael D. Laufer. A second Certificate of Correction dated November 13, 2007 (attached as Appendix E) corrected the priority claim of the '852 Patent to indirectly claim priority to U.S. Patent Application No. 08/833,550, filed on April 7, 1997, and now U.S. Patent No. 6,273,907. Copies of Maintenance Fee Payment Receipts are attached as Appendix F. There are no Reexamination Certificates.

**9. 37 C.F.R. §1.740(a)(9)**

Statement Showing that the '852 Patent Claims Methods of Treating Conditions of the Lungs, such as Severe Persistent Asthma, Using the Approved Product

As shown in the chart below, at least claims 1-7, 10-19, 32, 36, 41-49, 53 and 54 of the '852 Patent are directed to methods of using the approved product as set forth in the Catheter IFU, the Controller Operator's Manual ("Controller OM"), the FDA Executive Summary, and/or Panel Pack Sponsor Executive Summary (Sponsor Exec. Summ.) attached as Appendices B and G-I, respectively.

| Claim Element | Existence of the Claim Element in the Methods of Using the Approved Alair System |
|---|---|
| 1. A method for treating conditions of the lungs by decreasing airway responsiveness comprising: | The Alair System is used in methods for treating conditions of the lungs, such as severe persistent asthma, by decreasing airway responsiveness. (Catheter IFU at 5 and 17-19; Controller OM at 5; FDA Exec. Summ. at 3 and 6.) |
| transferring energy to or from an airway wall in the lungs to alter the airway wall in such a manner that the responsiveness of the airway is reduced. | The Alair System transfers RF energy to the airway wall and is intended to reduce ASM such that the responsiveness of the airway is reduced. (FDA Exec. Summ. at 6; Catheter IFU at 5; Controller OM at 5.) |
| 2. The method of claim 1, wherein the energy transfer alters the structure of the airway wall. | The bronchial thermoplasty caused by the Alair System is intended to reduce, debulk, or partially eliminate ASM, which alters the structure of the airway wall. (Catheter IFU at 5; Controller OM at 5.) |
| 3. The method of claim 1, wherein the energy transfer alters the function of the airway wall. | The reduction of ASM caused by the Alair System has been shown to alter the function of the airway wall by (a) decreasing the ability of the airways to constrict/contract, and/or (b) reducing responsiveness of the airway. (Catheter IFU at 5; Controller OM at 5.) |

| Claim Element | Existence of the Claim Element in the Methods of Using the Approved Alair System |
|---|---|
| 4. The method of claim 1, wherein the method is used to treat asthma by preventing contraction of the airway. | The Alair System treats asthma, at least in part, by decreasing the ability of the airways to constrict/contract. (Catheter IFU at 5; Controller OM at 5.) |
| 5. The method of claim 1, wherein the energy transfer alters the airway in such a manner that the ability of the airway to narrow is impaired. | The Alair System decreases the ability of the airways to constrict/contract and reduces the responsiveness of the airways, and therefore the transferred energy alters the airways in such a manner that the ability of the airway to narrow is impaired. (Catheter IFU at 5; Controller OM at 5.) |
| 6. The method of claim 1, wherein the energy is transferred to the airway by moving an energy transfer device along the airway. | In operation, the steps of placing the catheter in an airway, expanding the electrode array, activating the controller to deliver the RF energy, partially collapsing the electrode array, and moving the partially collapsed electrode array proximally in 5 mm increments are repeated along all, or at least a portion of, the length of an airway. (Catheter IFU at 17-19.) |
| 7. The method of claim 1, wherein the energy is transferred to a portion of the airway by an energy transfer device which creates one or more energy transfer patterns. | The Alair Catheter includes an expandable electrode array having four separate electrodes that create an energy transfer pattern having four elongated lines extending along at least a portion of the airway wall. (Catheter IFU at 14-19, and in particular Figures 5-7 and 11.) |
| 10. The method of claim 7, wherein the energy is transferred to the airway in a pattern of at least one stripe extending along the airway in a longitudinal or helical pattern. | The Alair Catheter delivers RF energy to the airway wall at 5 mm increments which are adjacent to each other to provide contiguous placement of the electrodes along the length of an airway. (Catheter IFU at 18-19, Figure 12.) As a result, the Alair System transfers energy to the airway in a pattern of four stripes that extend along at least a portion of the airway in a longitudinal pattern. |

| Claim Element | Existence of the Claim Element in the Methods of Using the Approved Alair System |
|---|---|
| 11. The method of claim 1, wherein the energy is transferred to the airway at the location of an opening of an airway, a bifurcation, or an opening of a side branch. | The electrode array of the Alair System is placed, among other areas, at an opening of an airway, a bifurcation, or an opening of a side branch as shown and described with reference to Figures 11 and 12 of the Catheter IFU. (Catheter IFU at 17-19.) The Alair System transfers RF energy to the airway at these locations. (Catheter IFU at 18-19.) |
| 12. The method of claim 1, wherein the energy is transferred to the airway at a segment of the airway between bifurcations, openings, or side branches. | The electrode array of the Alair System is placed at a segment between bifurcations, openings or side branches where it delivers energy as shown and described with reference to Figure 12 of the Catheter IFU. (Catheter IFU at 18-19.) |
| 13. The method of claim 1, wherein the energy is transferred to the airway by activating an energy transfer device, deactivating the energy transfer device, moving the energy transfer device, and reactivating the energy transfer device. | The Alair System operates by repeating the steps of placing the catheter in an airway, expanding the electrode array, activating the controller to deliver RF energy to the airway, partially collapsing the electrode array, and moving the catheter proximally by 5 mm increments along at least a portion of the length of the airway. (Catheter IFU at 18-19, Figure 12.) |
| 14. The method of claim 1, wherein the energy transfer alters smooth muscle of the airway wall in such a manner that the responsiveness of the airway is reduced. | The energy transferred to the airway wall by the Alair System is intended to reduce ASM such that the responsiveness of the airway is reduced. (Catheter IFU at 5; Controller OM at 5; FDA Exec. Summ. at 6.) |
| 15. The method of claim 14, wherein the ability of the smooth muscle to contract is altered. | The Alair System decreases the ability of the airways to constrict/contract, and since ASM is the portion of the airway that causes constriction, the Alair System alters the ability of the smooth muscle to contract. (Catheter IFU at 5; Controller OM at 5.) |

| Claim Element | Existence of the Claim Element in the Methods of Using the Approved Alair System |
|---|---|
| 16. The method of claim 15, wherein shortening of all or some of the smooth muscle is reduced or prevented. | The Alair System is intended to reduce, debulk or partially eliminate ASM such that the ability of the airway to constrict/contract is reduced. (Catheter IFU at 5; Controller OM at 5.) Since shortening of the ASM causes airway constriction, the Alair System reduces or prevents shortening of all or some of the smooth muscle. |
| 17. The method of claim 14, wherein the energy transfer alters a connection between the smooth muscle and the airway wall. | The Alair System is intended to reduce, debulk or partially eliminate ASM, and therefore it alters the connection between the ASM and the airway wall for the portion of the ASM that is reduced, debulked or partially eliminated. (Catheter IFU at 5; Controller OM at 5.) |
| 18. The method of claim 14, wherein the energy transfer eliminates at least a portion of the smooth muscle. | The energy transferred by the Alair System is intended to reduce, debulk or partially eliminate ASM. (Catheter IFU at 5; Controller OM at 5.) |
| 19. The method of claim 14, wherein the energy transfer prevents the smooth muscle from replicating. | The energy transferred by the Alair System is intended to reduce, debulk or partially eliminate the ASM, and therefore the energy transfer prevents the ASM from replicating. (Catheter IFU at 5; Controller OM at 5.) Moreover, the reduction in ASM mass persists over a long period indicating that the RF energy prevents the ASM from replicating. (Sponsor Exec. Summ. at 14-15.) |

| Claim Element | Existence of the Claim Element in the Methods of Using the Approved Alair System |
|---|---|
| 32. The method of claim 1, wherein the energy transfer alters at least a part of the epithelium in the airway wall. | In operation, the Alair Catheter is expanded until the electrodes contact the airway wall (Catheter IFU at 18-19, Figure 11), and RF energy is delivered through the electrode array to heat tissue to 65°C over the 5 mm area of exposed (uninsulated) electrode wire. (FDA Exec. Summ. at 5; and Sponsor Exec. Summ. at 15-16.) Because the electrodes directly contact the epithelium of the airway wall, the epithelium is heated to a temperature of 65°C, which alters the epithelium. |
| 36. The method of claim 1, wherein the energy transfer alters at least a part of a submucosal layer in the airway wall. | The Alair System heats tissue adjacent to the electrodes to 65°C to reduce, debulk, or partially eliminate ASM. (FDA Exec. Summ. at 5; Sponsor Exec. Summ. at 15-16; and Catheter IFU at 5.) Energy delivered at a controlled temperature of 65°C is sufficient to coagulate tissue without charring or vaporizing the tissue. The submucosal layer of the airway wall is located between the epithelium and the ASM, and thus the energy transferred by the Alair System will accordingly alter at least a portion of the submucosal layer in the airway wall. |
| 41. The method of claim 1, wherein the airways treated are at least 1 mm in diameter. | The Alair System is designed for treating airways of $\geq$ 3 mm in diameter. (Sponsor Exec. Summ. at 15-16.) |
| 42. The method of claim 41, wherein the airways treated are at least 3 mm in diameter. | The Alair System is designed for treating airways of $\geq$ 3 mm in diameter. (Sponsor Exec. Summ. at 15-16.) |
| 43. The method of claim 1, wherein the airways treated are generations 2 through 8. | The Alair System is designed for treating airways of $\geq$ 3 mm in diameter. (Sponsor Exec. Summ. at 15-16.) Airways of $\geq$ 3 mm in diameter include a portion of the range of generations 2 through 8. |

| Claim Element | Existence of the Claim Element in the Methods of Using the Approved Alair System |
|---|---|
| 44. The method of claim 43, wherein the airways treated are generations 2 through 6. | The Alair System is designed for treating airways of ≥ 3 mm in diameter. (Sponsor Exec. Summ. at 15-16.) Airways of ≥ 3 mm in diameter include a portion of the range of generations 2 through 6. |
| 45. The method of claim 1, wherein the airway treated are visualizable with a bronchoscope. | The bronchoscope is navigated to the target site and positioned so that the target site is in bronchoscopic view, and the catheter is advanced through the bronchoscope until the distal tip of the catheter shaft is in bronchoscopic view. (Catheter IFU at 17-18.) |
| 46. A method for treating conditions of the lungs by decreasing airway resistance to airflow comprising: | The Alair System is used in methods for treating severe persistent asthma by decreasing resistance to airflow. (Catheter IFU at 5 and 17-19; Controller OM at 5; and FDA Exec. Summ. at 3 and 6.) |
| transferring energy to or from an airway wall in the lungs to alter the airway wall in such a manner that a resistance to airflow of the airway is decreased. | The Alair System transfers RF energy to the airway wall and is intended to reduce ASM such that the resistance to airflow is reduced. (FDA Exec. Summ. at 6; Catheter IFU at 5; and Controller OM at 5.) |
| 47. The method of claim 46, wherein the energy transfer alters a structure of the airway wall to increase an effective caliber of the airway. | The Alair System reduces ASM and has been shown to increase the resting diameter of the airway. (Catheter IFU at 5; Controller OM at 5.) |
| 48. The method of claim 47, wherein the structure of the airway wall is altered by decreasing a thickness of the airway wall. | The bronchial thermoplasty caused by the Alair System is intended to reduce, debulk, or partially eliminate ASM, which alters the structure of the airway wall. (Catheter IFU at 5; Controller OM at 5.) |
| 49. The method of claim 46, wherein the energy transfer alters a function of the airway wall to increase an effective caliber of the airway. | The Alair System reduces ASM and has been shown to increase the resting diameter of the airway. (Catheter IFU at 5; Controller OM at 5.) |

| Claim Element | Existence of the Claim Element in the Methods of Using the Approved Alair System |
|---|---|
| 53. The method of claim 49, wherein the function of the airway wall is altered by altering a resting tone of the airway wall. | The reduction of ASM caused by the Alair System has been shown to (a) decrease the ability of the airways to constrict/contract, (b) reduce resistance to airflow, (c) reduce responsiveness of the airway, and/or (d) increase the resting diameter of the airway. (IFU at 5; OM at 5; and Sponsor Exec. Summ. at 14-16.) The energy from the Alair System accordingly alters the function of the airway wall. |
| 54. The method of claim 53, wherein the resting tone is altered by altering the smooth muscle or by denervation. | The Alair System has been shown to (a) decrease the ability of the airways to constrict/contract, (b) reduce resistance to airflow, (c) reduce responsiveness of the airway, and/or (d) increase the resting diameter of the airway by reducing, debulking or eliminating ASM. (IFU at 5; OM at 5; and Sponsor Exec. Summ. at 14-16.) |

**10. 37 C.F.R. §1.740(a)(10)**

Statement of the Relevant Dates and Information for Determination of the Application Regulatory Review

A clinical investigation on humans was conducted under Investigational Device Exemption (IDE) No. G050082, which received conditional approval on July 21, 2005. PMA No. P080032 was submitted to the FDA on December 30, 2008 and approved on April 27, 2010. The '852 Patent issued on June 25, 2002, and is currently set to expire on April 7, 2017.

**11. 37 C.F.R. §1.740(a)(11)**

Description of Significant Activities

During the applicable regulatory review period, the applicant was actively involved in obtaining premarket approval for the Alair System. As discussed above, IDE No. G050082 was conditionally approved on July 21, 2005, after which time clinical studies on humans were conducted with over 297 patients. PMA No. P080032 was submitted to the FDA in three modules; the last of the three modules was submitted on December 29, 2008 and subsequently amended eight times in response to questions from the FDA. PMA No. P080032 received an Advisory Panel Recommendation for Approval with Conditions on October 28, 2009. PMA No. P080032 was approved on April 27, 2010. A detailed description of the activities undertaken with respect to the Alair System during the regulatory review period is set forth in Appendix J.

**12. 37 C.F.R. §1.777(a)(12)**

Eligibility for Patent Extension and Length of Extension

In the opinion of the applicant Asthmatx, Inc., the '852 Patent is eligible for patent term extension because:

a. one or more of the claims of the '852 Patent claims methods of using the approved Alair System;

b. the term of the '852 Patent has not been extended on the basis of 35 U.S.C. §156 before submitting the present application for term extension;

c. the term of no other U.S. Patent has been extended under 35 U.S.C. §156 on the basis of the regulatory review process associated with the approved product;

d. there is an eligible period of regulatory review for which the patent may be extended pursuant to 35 U.S.C. §156;

e. the present application for term extension has been submitted within the 60-day period following the approval date of the approved product pursuant to 35 U.S.C. §156;

f. the owner of the '852 Patent, which was the applicant before the FDA for marketing approval, has authorized the present application for patent term extension of the '852 Patent; and

g. the present application for patent term extension complies with all requirements of 35 U.S.C. §156 and all applicable rules and regulations.

The period of patent term extension for the '852 Patent requested by the Applicant is **1,114 days**, such that the '852 Patent would expire on April 25, 2020. The requested extension

period of the '852 Patent corresponds to the regulatory review period for extension according to the provisions of 35 U.S.C. §156(g)(3), as calculated according to 37 C.F.R. §1.777.

A. Calculation Under 37 C.F.R. §1.777(c)(1)

The number of days in the period beginning on the date a clinical investigation on humans involving the device was begun (July 21, 2005) and ending on the date an application was initially submitted under Section 515 of the Federal Food, Drug and Cosmetic Act (December 29, 2008) was **1,257 days** (not including December 29, 2008).

B. Calculation Under 37 C.F.R. §1.777(c)(2)

The number of days in the period beginning on the date the application was initially submitted with respect to the device under Section 515 of the Federal Food, Drug and Cosmetic Act (December 29, 2008) and ending on the date such application was approved under such Act (April 27, 2010) was **485 days** (including December 29, 2008 and April 27, 2010).

The total regulatory review period under 37 C.F.R. §1.777(c) was **1,742 days**.

C. Adjustments Under 37 C.F.R. §1.777(d)(1)

Under 37 C.F.R. §1.777(d)(1), the regulatory review period eligible for extension is determined by subtracting the following from the regulatory review period calculated under 37 C.F.R. §1.777(c).

(i) The number of days in the periods of paragraphs (c)(1) and (c)(2) of 37 C.F.R. §1.777 which were on or before the date on which the patent issued.

**Subtract 0 days** - None of the days of the regulatory review period were on or before the June 25, 2002, issue date of the '852 Patent.

(ii) The number of days in the periods of paragraphs (c)(1) and (c)(2) of 37 C.F.R. §1.777 during which it is determined in 35 U.S.C. §156(d)(2)(B) by the Secretary of Health of Human Services that applicant did not act with due diligence.

**Subtract 0 days** - The Applicant acted with due diligence throughout the period from June 21, 2005, through April 27, 2010, as set forth in the detailed description of activities undertaken with respect to the Alair System in Appendix J. Further factual basis supporting the Applicant's due diligence includes:

(a) Debera Brown, Vice President of Regulatory Affairs at Asthmatx, Inc., is a corporate officer whose sole responsibility is handling of regulatory affairs;

(b) The Alair System is the sole product of Asthmatx, Inc., and therefore Ms. Brown devoted her full attention to regulatory review matters and handled such matters with dispatch throughout the entire regulatory review period; and

(c) Asthmatx, Inc. is not aware of any circumstances during the regulatory review period when it did not act with due diligence.

(iii) One-half the number of days remaining in the period defined by 37 C.F.R. §1.777(c)(1) after that period is reduced in accordance with paragraphs (d)(1)(i) and (ii) of this section, with half days being ignored for the purposes of subtraction.

**Subtract 628 days** - The relevant period of regulatory review eligible for patent term extension under 37 C.F.R. §1.777(d)(1) is accordingly **1,114 days (1,742 days - 628 days)**.

D. Calculations Under 37 C.F.R. §1.777(d)(2)

The number of days determined according to 37 C.F.R. §1.777(d)(1) are added to the original term of the patent, as shortened by any terminal disclaimer, to determine the extended term of the patent.

Extended Term of '852 Patent - **April 25, 2020** is the extended term of the '852 Patent, which is 1,114 days added to April 7, 2017.

E. Fourteen Year Limit Under 37 C.F.R. §1.777(d)(3-4)

Under 37 C.F.R. §1.777(d)(3-4), the extended term of the '852 Patent cannot exceed 14 years from the date of approval of PMA No. P080032, which is December 31, 2023. Therefore, extending the term of the '852 Patent to April 25, 2020 does not exceed the 14 year limit under 37 C.F.R. §1.777(d)(3-4).

F. Five Year Limit Under 37 C.F.R. §1.777(d)(5)

Under 37 C.F.R. §1.777(d)(5), the extended term of the '852 Patent cannot exceed five years form its original expiration date of April 7, 2017, which is April 7, 2022. Therefore, extending the term of the '852 Patent to April 25, 2020 does not exceed the 5 year limit under 37 C.F.R. §1.777(d)(5).

The applicant accordingly submits that the term of the '852 Patent should be extended to **April 25, 2020**.

**13. 37 C.F.R. §1.740(a)(13)**

Duty of Disclosure

Applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Human and Health Services or the Secretary of Agriculture any information which is material to the determination of entitlement to the patent term extension sought herein.

**14. 37 C.F.R. §1.740(a)(14)**

Prescribed Fee

Payment in the amount of $1,120 is submitted herewith accordance with 37 C.F.R. §1.20(j). Please charge any additional fee required in connection with the present application, throughout the pendency of this application, to Deposit Account # 50-0665.

**15. 37 C.F.R. §1.740(a)(15)**

Correspondence Information

All inquiries and correspondence relating to the present application for patent term extension should be directed to:

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(206) 359-3258
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**16. 37 C.F.R. §1.740(a)(16)**

Certified Duplicate of Application Papers

A duplicate of the application papers, certified as such, is submitted herewith.

Respectfully submitted,

Perkins Coie LLP

Date: 22 June 2010

Paul T. Parker
Registration No. 38,264

**Correspondence Address:**
Customer No. 46844
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Appendix A - FDA Approval Order PMA No. P0800032
Appendix B - Catheter Instructions for Use
Appendix C - U.S. Patent No. 6,411,852
Appendix D - Certificate of Correction (May 13, 2003)
Appendix E - Certificate of Correction (November 13, 2007)
Appendix F - Maintenance Fee Payment Receipts
Appendix G - Controller Operator's Manual
Appendix H - FDA Executive Summary P080032
Appendix I - Panel Pack Sponsor Executive Summary P080032
Appendix J - FDA Due Diligence Log

# Appendix A

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
10903 New Hampshire Avenue
Document Control Room W-066-0609
Silver Spring, MD 20993-0002

Ms. Debera Brown
Vice President, Regulatory Affairs
Asthmatx, Incorporated
888 Ross Drive, First Floor
Sunnyvale, California 94089

APR 27 2010

Re: P080032
Alair Bronchial Thermoplasty System: Alair Catheter and Alair RF Controller
Filed: December 30, 2008
Amended: January 6, February 4, February 17, June 9, June 11, June 25, October 1, October 9, 2009, December 11, 2009, and December 14, 2009
Procode: OOY

Dear Ms. Brown:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your premarket approval application (PMA) for the Alair Bronchial Thermoplasty System. This device is indicated for the treatment of severe persistent asthma in patients 18 years and older whose asthma is not well controlled with inhaled corticosteroids and long acting beta agonists. We are pleased to inform you that the PMA is approved. You may begin commercial distribution of the device in accordance with the conditions of approval described below.

The sale and distribution of this device are restricted to prescription use in accordance with 21 CFR 801.109 and under section 515(d)(1)(B)(ii) of the Federal Food, Drug, and Cosmetic Act (the act). The device is further restricted under section 515(d)(1)(B)(ii) of the act insofar as the labeling must specify the specific training or experience practitioners need in order to use the device. FDA has determined that these restrictions on sale and distribution are necessary to provide reasonable assurance of the safety and effectiveness of the device. Your device is therefore a restricted device subject to the requirements in sections 502(q) and (r) of the act, in addition to the many other FDA requirements governing the manufacture, distribution, and marketing of devices.

Expiration dating for this device has been established and approved at one year.

Continued approval of this PMA is contingent upon the submission of periodic reports, required under 21 CFR 814.84, at intervals of one year from the date of approval of the original PMA. Two copies of this report, identified as "Annual Report" and bearing the applicable PMA reference number, should be submitted to the address below. The Annual Report should indicate the beginning and ending date of the period covered by the report and should include the information required by 21 CFR 814.84.

In addition to the above, and in order to provide continued reasonable assurance of the safety and effectiveness of the device, the Annual Report must include, separately for the Alair Catheter and Alair RF Controller, the number of devices sold and distributed during the reporting period, including those distributed to distributors. The distribution data will serve as a denominator and provide necessary context for FDA to ascertain the frequency and prevalence of adverse events, as FDA evaluates the continued safety and effectiveness of the device.

In addition to the Annual Report requirements, you have agreed to provide the following data in post-approval study (PAS) reports. Two copies, identified as "PMA Post-Approval Study Report" and bearing the applicable PMA reference number, should be submitted to the address below.

1. The first post-approval study is to evaluate durability of effectiveness of the Alair System in patients with severe persistent asthma. The study population will consist of Alair-group subjects who are currently in the follow-up phase of the AIR2 Trial (Protocol #04-02).

   The primary endpoint of the PAS is the proportion of subjects experiencing severe exacerbations during the first year after the Alair treatment compared to subsequent 12-month periods out to 5 years. The study hypothesis to be evaluated is that the upper 95% confidence limit of the difference in proportions of subjects experiencing severe exacerbations (i.e., the subsequent 12-month proportion minus the first 12-month proportion) is less than 20%.

   The secondary endpoints will include the following additional safety endpoints for which data are currently being collected in the AIR2 Trial:
   - Severe exacerbation rates (exacerbations / subject / year)
   - Respiratory adverse events (rates of respiratory adverse events, and proportion of subjects with respiratory adverse events)
   - Emergency room visits for respiratory symptoms (rates of emergency room visits, and proportion of subjects with emergency room visits for respiratory symptoms)
   - Hospitalizations for respiratory symptoms (rates of hospitalizations, and proportion of subjects with hospitalizations for respiratory symptoms)
   - Respiratory Serious Adverse Events (detailed narratives will be provided for each event)
   - Forced Expiratory Volume in 1 second ($FEV_1$)

   For primary effectiveness endpoint, the primary analysis will test the hypothesis whether the upper 95% confidence limit of the difference in proportions of subjects experiencing severe exacerbations (i.e., the subsequent 12-month proportion minus the first 12-month proportion) is less than 20%. The proportions of patients with severe exacerbations at each year will be calculated with the denominator as the number of patients who complete follow-up visits for that particular year. Patients who are lost to follow-up will be excluded from the analysis.

In addition to the primary analyses, a sensitivity analysis will be conducted at 5 years.

Secondary effectiveness endpoints will be evaluated with descriptive statistics with 95% CI. All adverse events (AE) will be summarized by the number of the subjects reporting the adverse events, system organ class, preferred term, severity, relationship to procedure, and the duration of the AEs.

You have also agreed to make every reasonable effort to limit the cumulative loss-to-follow-up to be less than 20% at the 5 year follow-up (with an average yearly loss <5%). Beginning with the subjects entering the study at Year 2, and assuming a 20% dropout, approximately 140 subjects are expected to be evaluable for the 5-year endpoint.

2. The second PAS study will be a prospective, open-label, single arm, multi-center study conducted in the United States. The study objective is to demonstrate durability of treatment effect and to evaluate the short-term and longer-term safety profile of the Alair System in the United States in the intended use population. The sponsor will enroll up to 300 subjects (a minimum of 250 subjects) to achieve 200 evaluable study subjects at the end of 5 years post-treatment; this is based on a 20% lost-to-follow-up over 5 years.

   The primary endpoint will be the proportion of subjects experiencing severe exacerbations during the subsequent 12-month periods (for Years 2, 3, 4, and 5) compared to the first 12-month proportion after the Alair treatment. The study hypothesis is to demonstrate that the proportion of subjects who experience severe exacerbations in the subsequent 12-month follow-up [for Year 2, Year 3, Year 4 and Year 5 (in 12-month periods)] is not statistically worse when compared with the first 12-month proportion, which begins 6-weeks after the last Alair treatment. This objective will be met if the upper 95% confidence limit of the difference in proportions (i.e., the subsequent 12-month proportion minus the first 12-month proportion) is less than 20%.

   The secondary endpoints will include the following additional safety endpoints which will be evaluated annually through Year 5 following treatment with the Alair System:
   - Rates of Severe exacerbations (exacerbations / subject / year)
   - Respiratory adverse events (rates of respiratory adverse events, and proportion of subjects with respiratory adverse events)
   - Emergency room visits for asthma symptoms (rates of emergency room visits and proportion of subjects with emergency room visits for asthma symptoms)
   - Hospitalizations for asthma symptoms (hospitalizations/ subject/ year, and proportion of subjects with hospitalizations for respiratory symptoms)
   - Respiratory Serious Adverse Events (detailed narratives will be provided for each event)
   - Pre- and post-bronchodilator $FEV_1$

   The analysis plan for the primary and secondary effectiveness endpoints, and the AEs will be the same as described for the first PAS in this order.

You have also agreed to make every reasonable effort to limit the cumulative loss-to-follow-up to less than 20% at the 5 year follow-up (with an average yearly loss <5%). If the follow-up rate is unacceptably low during the 5 year follow-up, FDA will consider other options to limit loss-to-follow-up, including requiring you to recruit more subjects.

You must also update your patient and physician labeling (via PMA supplement) to reflect the results of the post-approval study at 5 years, as soon as these data are available, as well as any other time points deemed necessary by FDA if significant new information from the study becomes available.

Be advised that the failure to conduct any such study in compliance with the good clinical laboratory practices in 21 CFR part 58 (if a non-clinical study subject to part 58) or the institutional review board regulations in 21 CFR part 56 and the informed consent regulations in 21 CFR part 50 (if a clinical study involving human subjects) may be grounds for FDA withdrawal of approval of the PMA.

Within 30 days of your receipt of this letter, you must submit a PMA supplement that includes a complete protocol of your post-approval studies. Your PMA supplement should be clearly labeled as a "Post-Approval Study Protocol" and submitted in triplicate to the address below. Please reference the PMA number above to facilitate processing. If there are multiple protocols being finalized after PMA approval, please submit each protocol as a separate PMA supplement. For more information on post-approval studies, see the FDA guidance document entitled, "Procedures for Handling Post-Approval Studies Imposed by PMA Order" (www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070974.htm#2).

Before making any change affecting the safety or effectiveness of the device, you must submit a PMA supplement or an alternate submission (30-day notice) in accordance with 21 CFR 814.39. All PMA supplements and alternate submissions (30-day notice) must comply with the applicable requirements in 21 CFR 814.39. For more information, please refer to the FDA guidance document entitled, "Modifications to Devices Subject to Premarket Approval (PMA) - The PMA Supplement Decision-Making Process" (www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089274.htm).

You are reminded that many FDA requirements govern the manufacture, distribution, and marketing of devices. For example, in accordance with the Medical Device Reporting (MDR) regulation, 21 CFR 803.50 and 21 CFR 803.52, you are required to report adverse events for this device. Manufacturers of medical devices, including in vitro diagnostic devices, are required to report to FDA no later than 30 calendar days after the day they receive or otherwise become aware of information, from any source, that reasonably suggests that one of their marketed devices:

1. May have caused or contributed to a death or serious injury; or

2. Has malfunctioned and such device or similar device marketed by the manufacturer would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

Additional information on MDR, including how, when, and where to report, is available at www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm.

In accordance with the recall requirements specified in 21 CFR 806.10, you are required to submit a written report to FDA of any correction or removal of this device initiated by you to: (1) reduce a risk to health posed by the device; or (2) remedy a violation of the act caused by the device which may present a risk to health, with certain exceptions specified in 21 CFR 806.10(a)(2). Additional information on recalls is available at www.fda.gov/Safety/Recalls/IndustryGuidance/default.htm.

CDRH does not evaluate information related to contract liability warranties. We remind you; however, that device labeling must be truthful and not misleading. CDRH will notify the public of its decision to approve your PMA by making available, among other information, a summary of the safety and effectiveness data upon which the approval is based. The information can be found on the FDA CDRH Internet HomePage located at www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/PMAApprovals/default.htm. Written requests for this information can also be made to the Dockets Management Branch, (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. The written request should include the PMA number or docket number. Within 30 days from the date that this information is placed on the Internet, any interested person may seek review of this decision by submitting a petition for review under section 515(g) of the act and requesting either a hearing or review by an independent advisory committee. FDA may, for good cause, extend this 30-day filing period.

Failure to comply with any post-approval requirement constitutes a ground for withdrawal of approval of a PMA. The introduction or delivery for introduction into interstate commerce of a device that is not in compliance with its conditions of approval is a violation of law.

You are reminded that, as soon as possible and before commercial distribution of your device, you must submit an amendment to this PMA submission with copies of all approved labeling in final printed form. Final printed labeling that is identical to the labeling approved in draft form will not routinely be reviewed by FDA staff when accompanied by a cover letter stating that the final printed labeling is identical to the labeling approved in draft form. If the final printed labeling is not identical, any changes from the final draft labeling should be highlighted and explained in the amendment.

All required documents should be submitted in triplicate, unless otherwise specified, to the address below and should reference the above PMA number to facilitate processing. One of those three copies may be an electronic copy (eCopy), in an electronic format that FDA can

process, review and archive (general information: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/ucm134508.htm; clinical and statistical data: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/ucm136377.htm )

U.S. Food and Drug Administration
Center for Devices and Radiological Health
PMA Document Mail Center – WO66-G609
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

If you have any questions concerning this approval order, please contact Michael J. Ryan at 301-796-6283.

Sincerely yours,

Christy Foreman
Acting Director
Office of Device Evaluation
Center for Devices and Radiological Health
Food and Drug Administration

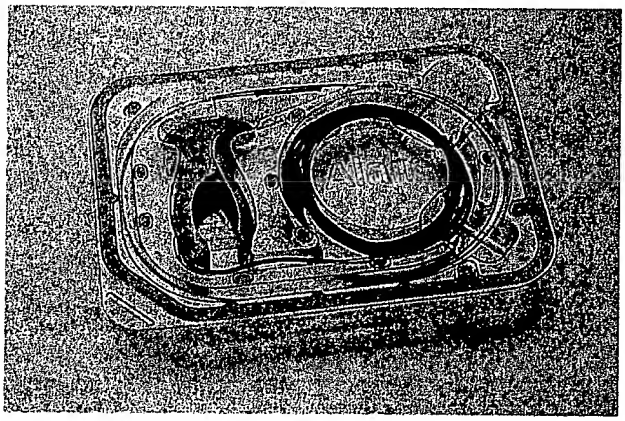
4/27/2010

# Appendix B

# ALAIR® | FOR BRONCHIAL THERMOPLASTY

## INSTRUCTIONS FOR USE

## Catheter Model ATS 2-5



| | |
|---|---|
| ℞ Only | United States federal law restricts this device to sale by or on the order of a physician. |
| ⚠ | The Alair® Catheter must be used by a physician who has training and experience in performing bronchoscopic procedures. |

**These Instructions for Use (IFU) are specific to the Alair® Catheter Model ATS 2-5. Do not attempt to operate the Alair® Catheter before thoroughly reading this IFU and the Alair® Radiofrequency Controller Model ATS 200 Operator's Manual.**

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# Table of Contents

## ALAIR® BRONCHIAL THERMOPLASTY SYSTEM DESCRIPTION

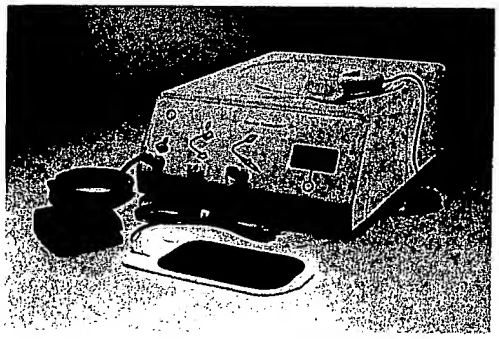

Figure 1: The Alair® Bronchial Thermoplasty System

**The Alair® Bronchial Thermoplasty System ("Alair® System"), manufactured by Asthmatx, Inc. ("Asthmatx"), consists of the Alair® Catheter and the Alair® Controller System, as described below:**

**Alair® Catheter:** The Alair® Catheter Model ATS 2-5 ("Catheter") is provided sterile and is a SINGLE-USE ONLY, disposable device. The Catheter delivers energy from the Controller to the desired site in the airway and relays temperature feedback to the Controller. The Alair® Catheter Model ATS 2-5 is designed to be used with the Alair® RF Controller Model ATS 200.

**Alair® Controller System**

**Alair® Radiofrequency (RF) Controller:** The Alair® RF Controller Model ATS 200 ("Controller") is designed to provide controlled delivery of RF energy to the Alair® Catheter. Energy from the Controller is delivered to the Catheter through the electrical cable attached to the proximal end of the catheter handle. Actual power delivered is automatically modulated by the Controller based on temperature control algorithms. The Controller delivers low-power, temperature-controlled RF energy to the airway at a predetermined temperature setting for a predetermined time period. The Controller incorporates hardware and software features that limit current, voltage, power, energy, time and temperature during each application of RF energy. The Controller is not intended to come in contact with the patient and therefore is not provided as a sterile device. For information on the installation, use, and other technical specifications, please read the Alair® Radiofrequency Controller Operator's Manual that is supplied with Model ATS 200.

**Footswitch:** The Controller is supplied with a footswitch that allows the operator to start and stop the delivery of RF energy. The Controller is designed to be used with the compatible footswitch provided by Asthmatx. The footswitch is not intended to come into contact with the patient and therefore is not provided as a sterile device.

**Patient Return Electrode:** The Controller is designed to be used with a gel-type patient return electrode that is compliant with the applicable portions of IEC 60601-2-2:2006 and/or CE marked. The patient return electrode is used to complete the return path for the electrical current. Use only patient return electrodes indicated for use with adults or patients weighing more than 15 kg (33 lbs). Examples of acceptable patient return electrodes include Valleylab E7506 and ConMed 51-7310. Follow the instructions for use (IFU) packaged with the patient return electrode.

## INDICATION FOR USE

The Alair® Bronchial Thermoplasty System is indicated for the treatment of severe persistent asthma in patients 18 years and older whose asthma is not well controlled with inhaled corticosteroids and long acting beta agonists.

## BRONCHOSCOPE REQUIREMENTS

The Catheter is designed to be used with high-frequency compatible flexible bronchoscopes that have a minimum 2.0mm working channel, and maximum 5.0mm outer diameter.

## MECHANISM OF ACTION

Airway smooth muscle (ASM) consists of muscle tissue within the airway walls in the lung. Contraction of the ASM is a main cause of airway constriction that leads to difficulty in breathing during asthma attacks. Severe asthma patients also experience an increase in ASM mass. This increase, together with inflammation of the airways, combines to thicken airway walls, which decreases the inside diameter of the airways when the ASM contracts. The resulting decrease in airway diameter causes increased resistance to airflow and further contributes to difficulty in breathing during asthma attacks.

The Alair® System is used to deliver thermal energy to the airway wall, to heat the tissue in a controlled manner in order to reduce ASM mass. Bronchial thermoplasty is intended to reduce, debulk, or partially eliminate smooth muscle tissue. In preclinical studies (Danek et al. 2004[1] , Brown et al. 2005[2] ), the reduction of ASM has been shown to decrease the ability of the airways to constrict/contract, reduce resistance to airflow and responsiveness of the airway, and increase the resting diameter of the airway.

## CONTRAINDICATIONS ⚠

Patients with the following conditions should not be treated:

- Presence of a pacemaker, internal defibrillator, or other implantable electronic devices,
- Known sensitivity to medications required to perform bronchoscopy, including lidocaine, atropine, and benzodiazepines,
- Patients previously treated with the Alair® System should not be retreated in the same area(s). No clinical data are available studying the safety and/or effectiveness of repeat treatments.

Patients should not be treated while the following conditions are present:

- Active respiratory infection,
- Asthma exacerbation or changing dose of systemic corticosteroids for asthma (up or down) in the past 14 days,
- Known coagulopathy,
- As with other bronchoscopic procedures, patients should stop taking anticoagulants, antiplatelet agents, aspirin and NSAIDS before the procedure with physician guidance.

1 Danek CJ, Lombard CM, Dungworth DL, Cox PG, Miller JD, Biggs MJ, Keast TM, Loomas BE, Wizeman WJ, Hogg JC, Leff AR. Reduction in airway hyperresponsiveness to methacholine by the application of RF energy in dogs. J Appl Physiol. 2004, 97(5):1946-53.

2 Brown RH, Wizeman W, Danek C, Mitzner W. Effect of bronchial thermoplasty on airway distensibility. Eur Respir J. 2005 Aug;26(2):277-82.

## WARNINGS ⚠

**READ THESE INSTRUCTIONS FOR USE IN CONJUCTION WITH THE ALAIR® RF CONTROLLER MODEL ATS 200 OPERATOR'S MANUAL BEFORE USING THE ALAIR® BRONCHIAL THERMOPLASTY SYSTEM. FAILURE TO FOLLOW ANY INSTRUCTIONS OR FAILURE TO HEED ANY WARNINGS OR PRECAUTIONS MAY RESULT IN HARM OR INJURY TO PATIENT.**

1. Prior to performing the procedure, ensure appropriate training, equipment, medications and staff are in place to handle any potential bronchoscopic, respiratory or anesthesia related emergencies. The Alair® System should only be used in a fully equipped bronchoscopy suite with access to full resuscitation equipment to handle hemoptysis, pneumothorax, and other respiratory complications including acute exacerbation of asthma and respiratory failure requiring intubation.
2. Do not deliver energy if the Catheter's electrode array is in contact with a metal object. This may result in harm or injury to the patient and/or operator.
3. Do not advance the Catheter within the bronchoscope if significant resistance is felt, as this may result in harm or injury to the patient and/or cause damage to the Catheter and/or bronchoscope.
4. Do not advance the Catheter into bronchi in which the Catheter cannot be seen under bronchoscopic vision. Advancing the Catheter beyond this region may cause patient harm or injury such as pneumothorax or pneumomediastinum.
5. Do not reposition the bronchoscope with the Catheter advanced beyond the distal end of the bronchoscope as this may result in patient harm or injury.
6. Use of the Alair® Catheter with a non-Alair® Controller may result in harm or injury to the patient and/or operator, or may result in product malfunction.
7. Do not treat the right middle lobe because of the potential susceptibility of the right middle lobe to transient obstruction as a result of inflammation or edema due to certain anatomical characteristics. The narrow diameter of the lobar bronchus and acute take-off angle may create poor conditions of drainage that may cause patient harm or injury such as atelectasis or difficulty in re-inflation (Right Middle Lobe Syndrome).

## PRECAUTIONS ⚠

1. The Alair® Catheter is provided sterile and is SINGLE USE ONLY. Do not use the Catheter if the package is opened, torn, or damaged. Use of a Catheter from damaged packaging may result in patient harm or injury. **Do not re-sterilize or reuse** the Catheter, as this may result in patient harm or injury, transmittal of infectious disease or product malfunction.
2. Do not use the Catheter if it comes in contact with a surface that is not aseptic (e.g. floor). This may result in patient infection.
3. Do not use the Catheter if it is damaged or irregular. Use of a damaged or irregular Catheter may result in patient harm or injury.
4. Do not use the Catheter if the marker bands are missing **(See Directions for Use, Figure 5)**.
5. Use care when handling the Catheter to avoid kinking the Catheter shaft.
6. Avoid deflecting the bronchoscope while the electrode array is within the bend of the bronchoscope's working channel as this may result in damage to the Catheter and failure of the Catheter to operate properly.
7. Before inserting or removing the Catheter from the bronchoscope, ensure the electrode array is relaxed. Do not use the Catheter if the electrode array does not expand or relax properly **(See Directions for Use, Figures 6 and 7)**.
8. Before delivering energy, make certain that all electrodes are in contact with the airway wall.

9. Caution should be taken in patients with the following conditions due to a potential increased risk of adverse events that may be associated with the procedure. Patients with these conditions were not studied in the pivotal trial and the safety of Alair® treatment for such patients has not been determined:

   - Post-bronchodilator $FEV_1$ < 65% predicted.
   - Other respiratory diseases including emphysema, vocal cord dysfunction, mechanical upper airway obstruction, cystic fibrosis or uncontrolled obstructive sleep apnea.
   - Use of short-acting bronchodilator in excess of 12 puffs per day within 48 hours of bronchoscopy (excluding prophylactic use for exercise).
   - Use of oral corticosteroids in excess of 10 milligrams per day for asthma.
   - Increased risk for adverse events associated with bronchoscopy or anesthesia, such as pregnancy, insulin dependent diabetes, epilepsy or other significant co-morbidities, such as uncontrolled coronary artery disease, acute or chronic renal failure, and uncontrolled hypertension.
   - Intubation for asthma, or ICU admission for asthma within the prior 24 months.
   - Any of the following within the past 12 months:
     i. 4 or more lower respiratory tract infections (LRTI)
     ii. 3 or more hospitalizations for respiratory symptoms
     iii. 4 or more OCS pulses for asthma exacerbation

10. The Alair® System should only be used by clinicians who are experienced in bronchoscopy and have undergone adequate training with the device.
11. The Alair® System should only be used in patients stable enough to undergo bronchoscopy in the judgment of their clinician.
12. Follow local governing ordinances and your institution's biohazard procedures regarding disposal of the Alair® Catheter and patient return electrode.

## CLINICAL DATA

### *Objectives*

The pivotal study was a multi-center, randomized, double-blind, sham-controlled study to demonstrate the safety and effectiveness of the Alair® System in a population of subjects with severe asthma.

### *Effectiveness Endpoints*

The primary effectiveness endpoint was the difference between treatment (Alair) and control (Sham) groups in the change in the Asthma Quality of Life Questionnaire (AQLQ) score between baseline and the average of 6-, 9-, and 12-month follow-up visits (integrated AQLQ score). Other endpoints included: rates of severe asthma exacerbations, proportions of patients with severe asthma exacerbations, and days lost from work, school, or other daily activities due to asthma symptoms. In addition, several safety endpoints were considered for effectiveness; these endpoints included rates of asthma (multiple symptoms)* adverse events, Unscheduled Physician Office visits for respiratory symptoms, Emergency Room visits for respiratory symptoms, and Hospitalizations for respiratory symptoms.

* "Asthma (multiple symptoms)" is defined as occurrence or worsening of shortness of breath, wheeze, cough, productive cough, or some combination of these.

### *Methods*

This was a multicenter, randomized (2 Alair, 1 Sham), double-blind, sham-controlled clinical trial comparing the effects of treatment with the Alair® System to a Sham treatment in subjects that were optimized to conventional therapy of inhaled corticosteroids (ICS) and long-acting $\beta_2$-agonists (LABA). All subjects included in the Study were taking ICS (> 1000µg beclomethasone or equivalent per day) and LABA (≥ 100µg salmeterol or equivalent per day), and were still symptomatic.

Subjects in the Alair and Sham groups were administered the Alair® treatment and Sham bronchoscopies, respectively, by an unblinded bronchoscopy team in 3 separate bronchoscopy sessions. Each bronchoscopy session was separated by at least 3 weeks. All bronchoscopy sessions were administered under local anesthesia with sedation. Subjects had follow-up visits with blinded asthma assessment teams at 6-weeks, 12-weeks, 6-months, 9-months, and 12-months after the final bronchoscopy session.

All subjects were prescribed to take 50mg of oral prednisone or prednisolone (or equivalent) each day for 5 days covering the 3 days before the bronchoscopy session, the day of the bronchoscopy session, and the day after the bronchoscopy session (prophylactic indication).

### *Statistical Plan*

Primary and secondary endpoints, as well as adverse events were analyzed using Bayesian statistics. The Posterior Probability of Superiority was calculated for the primary and secondary endpoints, as well as safety outcomes.

### *Patient Population*

Enrollment was limited to patients with severe persistent asthma who were still symptomatic despite being managed on conventional therapy of high dose ICS and LABA. Subjects may have been taking up to 10 milligrams of oral corticosteroids per day. Study subjects were required to meet the following patient selection criteria:

**Key Entry Criteria**

**Inclusion**

1. Adult; age 18-65 years.
2. Asthma requiring regular maintenance medication that includes inhaled corticosteroids (greater than 1000µg beclomethasone per day or equivalent) and long-acting $\beta_2$-agonists (at least 100µg salmeterol per day or equivalent), with or without other asthma medications. Oral corticosteroids at a dosage of up to, but not greater than 10mg per day, or 20 milligrams every other day are acceptable.
3. Asthma Quality of Life Questionnaire Score during the Baseline Phase of 6.25 or less.
4. Pre-bronchodilator forced expiratory volume in one second ≥60% predicted (after patients stabilized on inhaled corticosteroids and long-acting $\beta_2$-agonists during the Baseline Phase).
5. Non-smoker x 1 year or greater (if former smoker, less than 10 pack years total smoking history).

**Exclusion**

1. Post-bronchodilator $FEV_1$ <65% predicted.
2. Three or more hospitalizations for exacerbations of asthma in the previous year; OR a history of life-threatening asthma, defined by past intubations for asthma, or intensive care unit admission for asthma within the prior 24 months.
3. History of recurrent lower respiratory tract infection requiring antibiotics (more than 3 in the past 12-Months).
4. History of recurrent oral steroid use for asthma (4 or more pulses of oral steroids in the past 12-Months).

***Demographics***

A total of 297 subjects between the ages of 18 and 65 were enrolled and randomized (2 Alair: 1 Sham) in this study. One hundred and ninety (190) subjects received the Alair® treatment and 98 subjects received the Sham control treatment (Intent-to-Treat population). The Sham procedure was identical to the Alair® procedure except that no energy was delivered through the Catheter.

There were no statistical differences in demographic measures between the Alair and Sham groups. Subject demographics are described in **Table 1.**

| | **Alair (n=190)** | **Sham (n=98)** |
|---|---|---|
| Age (years) (Mean ± SD) | 41 ± 12 | 41 ± 12 |
| Gender | | |
| Male | 81 (43%) | 38 (39%) |
| Female | 109 (57%) | 60 (61%) |
| Race/Ethnicity | | |
| Caucasian | 151 (80%) | 72 (74%) |
| African American / Black | 19 (10%) | 15 (15%) |
| Hispanic | 6 (3%) | 4 (4%) |
| Asian | 4 (2%) | 1 (1%) |
| Other | 10 (5%) | 6 (6%) |
| Height (cm) (Mean ± SD) | 167 ± 9 | 167 ± 10 |
| Weight (kg) (Mean ± SD) | 82 ± 18 | 82 ± 20 |

**Table 1: Subject Demographics (Intent-to-Treat Population)**

***Effectiveness Results***

Effectiveness analyses were performed for both the Intent-to-Treat (ITT) population and Per-Protocol (PP) population. The ITT population consisted of all randomized subjects who have been administered at least one bronchoscopy. The PP population excluded all subjects in the ITT population who met any of the following criteria:

- Have taken any interfering concomitant medications.
- Have undergone other interfering treatments.
- Did not attend one of the 6-, 9-, 12-month visits, with the exception of a discontinuation from the Study due to an adverse event related to Study treatment.
- Had missed one or more bronchoscopy procedures.

***Effectiveness Endpoints***

Although the clinical study was powered only for the primary effectiveness endpoint (see below), several effectiveness endpoints and safety endpoints that could also be considered effectiveness endpoints demonstrated clinically meaningful differences in favor of the Alair group compared to the Sham group. The effectiveness endpoints were rates of severe asthma exacerbations, proportions of patients with severe asthma exacerbations, and days lost from work, school, or other daily activities due to asthma symptoms. The safety endpoints considered for effectiveness were rates of asthma, emergency room visits for respiratory symptoms, and hospitalization rates for respiratory symptoms.

**Steroid Exacerbations[a] (Severe Exacerbations Requiring Systemic Corticosteroids) (ITT Population)**

During the Post-Treatment Phase, the severe exacerbation rate for the Steroid Exacerbations was 0.48 exacerbations/subject/year in the Alair group and 0.70 exacerbations/subject/year in the Sham group [95% CI (Sham - Alair): -0.031, 0.520]. During the Post-Treatment Phase, the proportion of subjects experiencing Steroid Exacerbations was 26% in the Alair group and 40% in the Sham group [95% CI (Sham - Alair): 2.1%, 25.1%].

Steroid Exacerbation rates (annualized rate) and proportion of patients experiencing Severe Exacerbations for the Post-Treatment Phase are presented graphically in **Figure 2**.

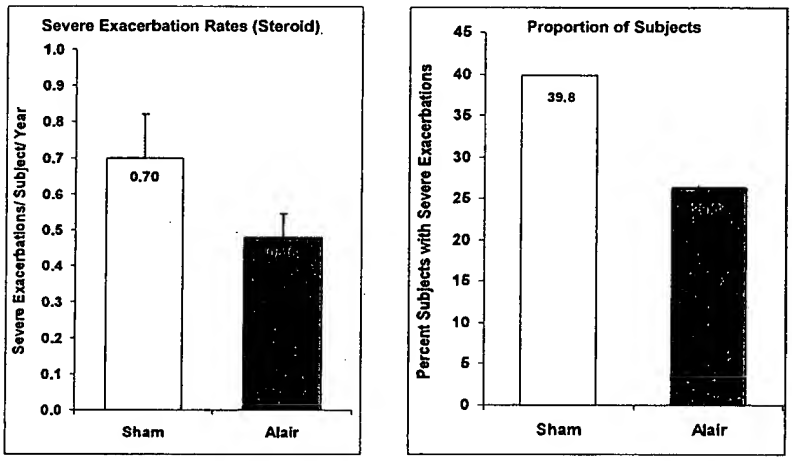


**Figure 2: Severe Exacerbations during the Post-Treatment Phase**

[a] **Steroid Exacerbations** = Exacerbations treated with oral or intravenous corticosteroids, OR a doubling of the baseline inhaled corticosteroid dose for at least 3 days, OR any temporary increase in the dosage of oral corticosteroids for a subject taking maintenance oral corticosteroids at Study entry.

Annualized rates of exacerbations per subject are extrapolated from the 46 week Post-Treatment Phase from 6 weeks after the last bronchoscopy procedure to the 12 month follow-up visit.

**Days Lost from Work, School, or Other Daily Activities due to Asthma Symptoms (ITT Population)**

During the Post-Treatment Phase, subjects in the Alair group lost an average of 1.3 days/year/subject from work, school, or other daily activities due to asthma symptoms, compared to the Sham group that lost 3.9 days/year/subject (annualized rates per subject are extrapolated from the 46 week Post-Treatment Phase from 6 weeks after the last bronchoscopy procedure to the 12 month follow-up visit) [95% CI (Sham - Alair): 0.425, 6.397].

## Safety Endpoints that Demonstrated Effectiveness

Measures such as Emergency Room visits and Hospitalizations for respiratory symptoms are generally considered to be important measures of safety, especially if an intervention results in an increase in the rate of one or more of these events. However, these measures can also be considered important measures of effectiveness if an intervention results in a measurable decrease in the rate of one or more of these events. During longer-term follow-up (> 6 weeks after the last Alair® treatment), there was a reduction in asthma (multiple symptoms) adverse events [95% CI (Sham - Alair): -0.01, 0.001], Emergency Room visits for respiratory symptoms [95% CI (Sham - Alair): 0.11, 0.83], and Hospitalizations for respiratory symptoms (event rate per group) [95% CI (Sham - Alair): 0.025, 0.172], presented graphically in **Figure 3**.

There was a reduction in the proportion of subjects having asthma (multiple symptoms) adverse events [95% CI (Sham - Alair): 4.0%, 27.3%], and in the proportion of subjects having Emergency Room visits for respiratory symptoms in the Alair group (3.7% in the Alair group compared to 15.3% in the Sham group) [95% CI (Sham - Alair): 4.6%, 19.7%].

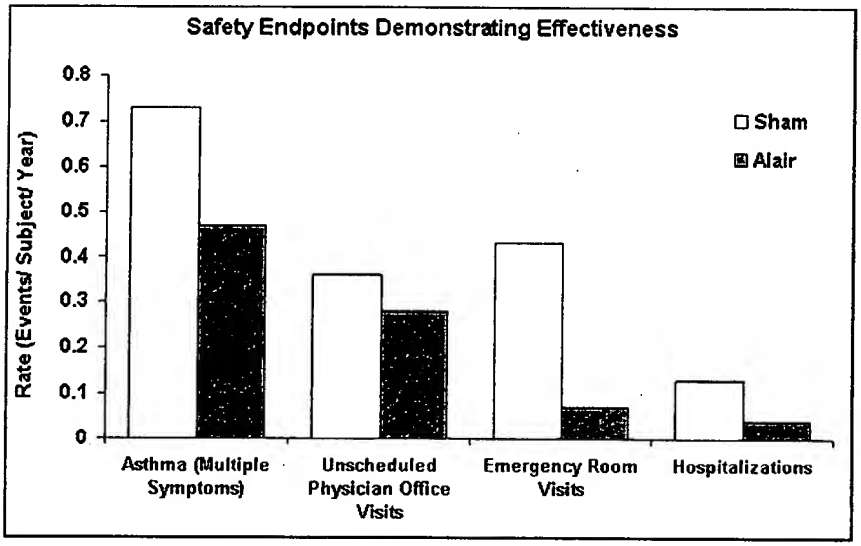


**Figure 3: Safety Endpoints demonstrating Effectiveness (ITT Population)**

### *Primary Effectiveness Endpoint – Integrated AQLQ Score*

The difference between the Alair and Sham groups in the average change in AQLQ score from Baseline at the 6-, 9-, and 12-month follow-up visits was 0.210 [95% CI (Alair - Sham): -0.025, 0.445]. The pre-specified Posterior Probability of Superiority for the difference between the groups was 96.4%. For the ITT population, the difference between the groups had a Posterior Probability of Superiority of 96.0%, and for the PP population, the difference between the groups had a Posterior Probability of Superiority of 97.9%, demonstrating an improvement in the Asthma Quality of Life in the Alair group compared to Sham.

The results for the change from Baseline of the Integrated AQLQ score for the Intent-to-Treat and Per Protocol populations are summarized in **Table 2**.

| Population | Difference Between Groups in Integrated AQLQ Score (Posterior Mean, 95% CI) | Posterior Probability of Superiority (%) |
|---|---|---|
| **ITT (Intent-to-Treat)** (Alair N=190, Sham N=98) | 0.210 (-0.025, 0.445) | 96.0 |
| **PP (Per Protocol)** (Alair N=173, Sham N=95) | 0.244 ( 0.009, 0.478) | 97.9 |

**Table 2: Primary Effectiveness Endpoint: Integrated AQLQ Score**

## ADVERSE EVENTS IN PIVOTAL STUDY

### *Patient Population*

The Alair® System was evaluated in a randomized, double-blind, sham-controlled, multi-center clinical study – the Asthma Intervention Research 2 (AIR2) Trial. A total of 297 subjects with severe persistent asthma who were still symptomatic despite being managed on conventional therapy of high dose ICS and LABA were randomized – 196 subjects in the Alair group and 101 subjects in the Sham group. (See the Clinical Data section for key entry criteria.) The Sham procedure was identical to the Alair® procedure except that no energy was delivered to the Catheter in the sham procedure.

Safety analyses were performed for the Intent-to-Treat (ITT) population (288 subjects) that consisted of all randomized subjects who have been administered at least one bronchoscopy.

### *Observed Adverse Events*

The safety of the Alair® System was assessed by comparing adverse event profiles of the Alair and Sham group subjects. Adverse event profiles are compared for the Treatment Phase (day of first bronchoscopy procedure to 6 weeks after the last bronchoscopy procedure) and Post-Treatment Phase (6 weeks after the last bronchoscopy to the 12 month follow-up visit).

Adverse events (whether considered procedure-related or not procedure-related by the investigator) occurring with ≥ 3% incidence that were more common in the Alair group are presented for 288 patients in **Table 3**.

| Adverse Event | Treatment[3] | | Post-Treatment[4] | |
|---|---|---|---|---|
| | Alair (N=190) % | Sham (N=98) % | Alair (N=187) % | Sham (N=98) % |
| **Average duration of period (days)** | 84 | | 322 | |
| **Ear, Nose, and Throat** | | | | |
| Upper respiratory tract infection | 20 | 11 | 30 | 26 |
| Viral Upper respiratory tract infection | 4 | 2 | 6 | 7 |
| Nasopharyngitis | 5 | 7 | 11 | 5 |
| Acute Sinusitis | 3 | 2 | 4 | 8 |
| Rhinitis | 2 | 0 | 4 | 6 |
| **Lower Respiratory** | | | | |
| Asthma (Multiple Symptoms) | 52 | 39 | 27 | 43 |
| Wheezing | 15 | 6 | 4 | 3 |
| Dyspnea | 11 | 6 | 2 | 1 |
| Bronchitis | 4 | 2 | 7 | 5 |
| Chest discomfort | 9 | 10 | 2 | 1 |
| Atelectasis | 5 | 0 | 0 | 0 |
| Hemoptysis | 3 | 0 | 0 | 0 |
| Lower respiratory tract infection | 8 | 2 | 3 | 6 |
| Chest pain | 14 | 13 | 3 | 1 |
| **Neurology** | | | | |
| Anxiety | 4 | 0 | 1 | 2 |
| Headaches | 14 | 9 | 5 | 3 |
| **Gastrointestinal** | | | | |
| Dyspepsia | 4 | 2 | 2 | 4 |
| Nausea | 3 | 4 | 1 | 1 |
| **Non-site specific** | | | | |
| Pyrexia (fever) | 4 | 2 | 0 | 1 |
| Influenza | 4 | 2 | 4 | 12 |
| **Other** | | | | |
| Urinary tract infection | 1 | 1 | 3 | 1 |
| Hypertension | 3 | 2 | 3 | 3 |

**Table 3: Adverse Events with ≥ 3% Incidence (% of subjects) that were more common in the Alair Group**

**Adverse events occurring in both the Treatment Phase and Post-Treatment Phase at a rate of <3% and ≥1% (whether considered procedure-related or not procedure-related by the investigator) that were more frequently reported by the Alair group than the Sham group included pneumonia, operative hemorrhage, abnormal breath sounds, bronchial obstruction, acute bronchitis, bronchospasm, lower respiratory tract infection (viral), pulmonary congestion, discolored sputum (blood-tinged sputum), increased upper airway secretion, and viral pharyngitis.**

During the Treatment Phase in the AIR2 Trial, there was a transient increase in respiratory adverse events, including asthma (multiple symptoms), upper respiratory tract infection, atelectasis, lower respiratory tract infection, wheezing, hemoptysis, and anxiety in the Alair group compared to the Sham group. There was a lower incidence of throat irritation in the Alair group compared to the Sham group. There were 7 instances of hemoptysis defined as >5.0 mL (1.3% of bronchoscopies) of which 2 occurred on the day of the procedure, 2 occurred within 3 days, 2 occurred at 2 weeks, and one occurred on Day 31 after the procedure. The greatest amount of hemoptysis observed was a cumulative total of 150 mL that occurred over 5 days and was treated with bronchial artery embolization.

During the Treatment Phase (~ 12 weeks period), the rate of Unscheduled Physician Office visits (events / subject / 12 weeks) in the Alair group was 0.230 compared to 0.133 in the Sham group. The rate of hospitalizations for respiratory symptoms (events / subject / 12 weeks) was 0.086 in the Alair group compared to 0.028 in the Sham group. The rate of Emergency Room visits for respiratory symptoms (events / subject / 12 weeks) was 0.062 in the Alair group compared to 0.075 in the Sham group.

[3] Treatment phase represents adverse events reported between the first bronchoscopy and 6-weeks post last bronchoscopy
[4] Post-Treatment phase represents adverse events reported between 6-weeks post last bronchoscopy and the 12 month visit

During the Post-Treatment Phase in the AIR2 Trial, there was a lower incidence of respiratory symptoms in the Alair group compared to the Sham group, including a 36% reduction in asthma (multiple symptoms) events and proportion of subjects with asthma (multiple symptoms) events. There was also a lower incidence of influenza, and a greater incidence of nasopharyngitis, in the Alair group compared to the Sham group.

### High Resolution Computed Tomography (HRCT) Results

In the 150 subjects (100 Alair group and 50 Sham group) assigned to HRCT scan examinations, at 1-year, there were no difference in signs of gas trapping or consolidation and there was no evidence of bronchiectasis. A difference was seen in bronchial wall thickening without gas trapping which occurred only in the Sham subjects (4%).

### Summary of Clinical Findings

Results from the clinical study which evaluated the effectiveness and safety of the Alair® System in subjects with severe asthma demonstrated that Alair® treatment resulted in clinically significant reductions in severe exacerbations that required systemic steroids, the percent of subjects experiencing the severe exacerbations, the number of Emergency Room visits for respiratory symptoms, the percent of subjects experiencing Emergency Room visits for respiratory symptoms, Hospitalizations for respiratory symptoms, and days lost from school/work/other daily activities due to asthma symptoms. Although bronchial thermoplasty was associated with an increased rate of respiratory adverse events during the Treatment Phase (primarily related to asthma), in the Post-Treatment Phase, a smaller proportion of patients treated with bronchial thermoplasty experienced respiratory adverse events, including asthma (multiple symptoms).

## DIRECTIONS FOR USE

### Alair® Catheter Inspection and Preparation

1. The Alair® System should only be used by a physician trained in bronchoscopy. These instructions do not explain bronchoscopic procedures.
2. Please read the Operator's Manual for the Alair® RF Controller Model ATS 200 before beginning the procedure.
3. Visually inspect the package for damage before removing the Catheter from the package. Do not use the Catheter if the package is damaged or has been previously opened or torn.
4. Aseptically remove the Catheter from the package tray and inspect for any damage. The Catheter is packaged with the electrode array retracted within the protective, removable orange-colored Catheter tip sheath. Before use, remove the protective orange sheath. Inspect the Catheter for any damage such as broken or crushed areas of the Catheter, sharp or protruding edges at the distal tip, or any excessive bends or kinks in the Catheter shaft. Do not use the Catheter if any damage or irregularity is found. See **Figure 4**.

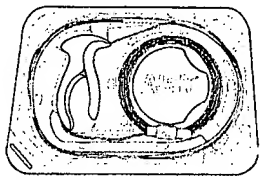

**Figure 4: Alair® Catheter In Tray**

5. The distal portion of the Catheter shaft has marker bands that are spaced 5mm apart to aid in the positioning of the Catheter electrode array. Do not use the Catheter if the marker bands are missing. See **Figure 5**.

**Figure 5: Alair® Catheter with its four Marker Bands, spaced 5mm apart**

6. Hold the Catheter handle in the palm of your hand, with the thumb and forefinger just below the Alair® logo. Then, squeeze the forward handle back towards the back handle, ensuring that the electrode array expands properly. Verify that the electrode array opens fully and evenly. See **Figure 6**.

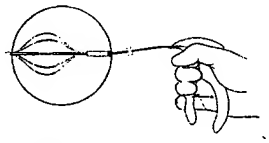

**Figure 6: Alair® Catheter Electrode Array Expanded**

7. Relax the electrode array by releasing the front handle. See **Figure 7**. Do not use the Catheter if the electrode array does not expand or relax properly.

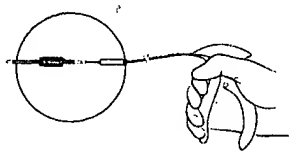

**Figure 7: Alair® Catheter Electrode Array Relaxed**

### *Alair® Bronchial Thermoplasty System Set-up and Operation*

The Alair® Catheter is intended to be used in conjunction with the Alair® Controller. Please read the Alair® RF Controller Model ATS 200 Operator's Manual before using the Alair® System.

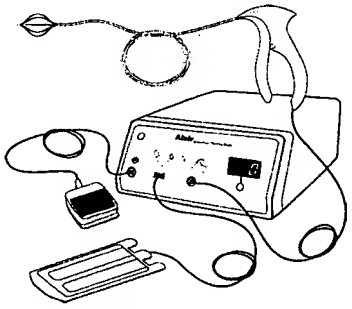

**Figure 8** illustrates the Alair® RF Controller Model ATS 200 set up.

Consult the Alair® RF Controller Model ATS 200 Operator's Manual for specific instructions on:

- Controller Installation;
- Controller Power-Up;
- Connection of Components and Accessories;
- Controller Modes;
- Periodic Maintenance and Repair;
- Troubleshooting; and
- Technical Specifications.

### *Patient Preparation*

1. Administer prophylactic prednisone or equivalent at a dosage of 50 mg/day for the 3 days before the procedure, the day of the procedure and the day after the procedure to minimize post procedure inflammation.

2. Verify the patient remains a good candidate for bronchoscopy under moderate sedation prior to initiation of the procedure (Mayse et al 2007)[5]. Postpone the procedure if any of the following conditions apply:

    - Prescribed prednisone was not taken on the 3 days before bronchoscopy.
    - $SpO_2$ is less than 90% on room air.
    - Increase in asthma symptoms in last 48 hours requiring more than 4 puffs/day on average of rescue bronchodilator over pretreatment usage.
    - Asthma exacerbation or changing dose of systemic corticosteroids for asthma (up or down) in the past 14 days.
    - Active respiratory infection, active allergic sinusitis, or other clinical instability.
    - Physician feels for any reason the procedure should be postponed.

[5] Mayse ML, Laviolette M, Rubin AS, Lampron N, Simoff M, Duhamel D, Musani, AI, Yung RC, Mehta AC. Clinical Pearls for Bronchial Thermoplasty. J Bronchol. 2007, 14:115-123.

3. Prepare the patient for bronchoscopy. Follow patient management protocols according to staffing, training, and individual institution-specific policies and guidelines for bronchoscopy.
4. Place the patient return electrode securely on the patient in accordance with manufacturer's instructions.
5. Introduce the flexible bronchoscope through the nose or mouth as appropriate. See **Figure 9** below.

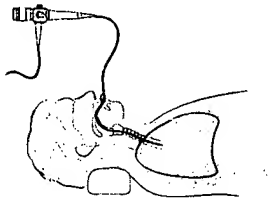

**Figure 9: Bronchoscope navigation into patient's airways**

6. Navigate the bronchoscope to the targeted site and position the bronchoscope so that the targeted site is in bronchoscopic view.

### *Alair® Catheter Use*

1. Before inserting the catheter into the bronchoscope, ensure the electrode array is relaxed.
2. Advance the catheter into the bronchoscope working channel *being careful not to kink the catheter shaft.* Kinking of the catheter shaft could result in failure of the catheter electrode array to open fully in tortuous anatomy. See **PRECAUTIONS**.
3. Avoid deflecting the bronchoscope while the electrode array is within the bend of the bronchoscope's working channel as this could result in damage to the Catheter and failure of the Catheter to operate properly. See **PRECAUTIONS**.
4. Advance the Catheter through the bronchoscope until the distal tip of the Catheter shaft is in bronchoscopic view. If the device encounters significant resistance during insertion, do not force it. In especially tortuous anatomy it may be necessary to relax the bronchoscope's deflection mechanism until the device passes smoothly. See **Figure 10** below.

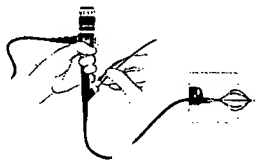

**Figure 10: Alair® Catheter introduced through working channel of bronchoscope**

5. Advance the Catheter to the targeted site under bronchoscopic vision. Do not advance the Catheter into bronchi in which the Catheter cannot be seen under bronchoscopic vision. Advancing the Catheter under such conditions may result in pneumothorax, pneumomediastinum or other harm or injury to the patient. See **WARNINGS**.
6. Do not treat the right middle lobe because of the potential susceptibility of the right middle lobe to transient obstruction as a result of inflammation or edema due to certain anatomical characteristics. The narrow diameter of the lobar bronchus and acute take-off angle may create poor conditions of drainage that may cause patient harm or injury such as atelectasis or difficulty in re-inflation (Right Middle Lobe Syndrome). See **WARNINGS**.
7. Do not reposition the bronchoscope with the Catheter advanced beyond the distal end of the bronchoscope as this may result in harm or injury to the patient. See **WARNINGS**.

8. Once at the targeted site, squeeze the handle together to expand the electrode array partially so that the electrodes are close to or just touching the targeted site.

9. With the electrode array partially expanded, adjust the axial position of the electrodes in the airway to position the active electrodes (exposed 5mm center region of the array electrodes) as desired. Expand the array until all four electrodes firmly contact the airway wall. *Do not over-expand the electrode array* as this may cause one or more of electrodes to deploy inward or 'invert'. If an electrode inverts, relax the electrode array and then re-expand the array in a large, straight airway, confirming proper deployment before returning to the area being treated. In most cases, full expansion of the Catheter electrode array will NOT require the catheter handle to be squeezed completely.

10. Proper contact of the electrodes with the airway wall should be confirmed visually. See **Figure 11** below.

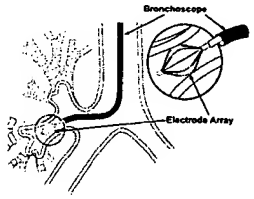


**Figure 11: Alair® Catheter in the Airway**

11. Before delivering RF energy, make certain that all electrodes are in contact with the airway wall. See **PRECAUTIONS**.

12. Deliver RF energy to the targeted region by pressing and releasing the footswitch once. The Controller will deliver energy automatically according to preset parameters for time, energy, power, and temperature.

13. To manually terminate RF energy delivery, if necessary, press and release the footswitch again.

    ***Note:*** *The Controller will automatically shut off the RF energy if it detects atypical energy delivery or temperature response.*

14. The Controller is programmed to alert the user with both audible and visual cues if re-deployment of the electrode array or replacement of the Catheter is required. Please refer to the Alair® RF Controller Model ATS 200 Operator's Manual for more detailed instructions on these audible sounds and light displays.

    ***Note:*** *If RF energy delivery ends prematurely, it may be necessary to re-deploy the electrode array and begin RF energy delivery again. If the problem persists, replace the Catheter.*

15. Reposition the Catheter and repeat the steps above making 5mm proximally placed contiguous treatments. The catheter's marker bands are spaced 5mm apart to assist with contiguous placement. See **Figure 12**.

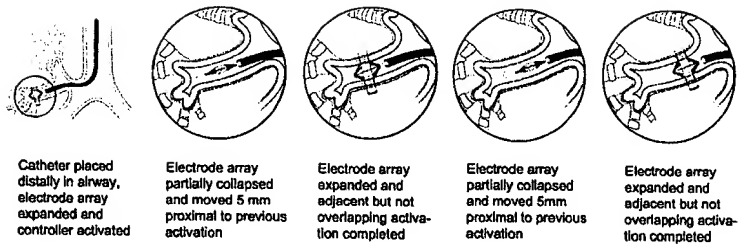


**Figure 12: Contiguous Placement and Activation**

16. Once the procedure is complete, relax the Catheter handle to relax the electrode array before removing the Catheter from the bronchoscope or before withdrawing the Catheter into the bronchoscope for airway navigation. To manipulate the bronchoscope with the Catheter in the working channel, withdraw the Catheter approximately 10 cm into the bronchoscope so the electrode array is proximal to the bend in the distal tip of the bronchoscope.
17. Once the treatment is complete, remove the Catheter from the bronchoscope. Disconnect the Catheter from the Controller, and dispose of the used Catheter per your institution's biohazard procedures. Remove the return electrode from the patient. Disconnect the patient return electrode from the Controller, and dispose of the patient return electrode per your institution's biohazard procedures.

***Post Procedure Care***

1. Follow appropriate institutional guidelines for post procedure care. It is recommended that patients should be carefully monitored and discharged only after they are deemed to be stable and have adequate (comparable to pre-procedure) lung function, mental status, and are able to adequately take liquids.

2. Recommended post procedure assessments are based on the criteria that were used in clinical trials of bronchial thermoplasty (Mayse et al 2007) and include:

    - 2 to 4 hour recovery/monitoring period following each procedure
    - Spirometry, breath sounds, and vital signs (heart rate, blood pressure, temperature, respiratory rate, pulse oximetry) before discharge
    - Discharge if post bronchodilator $FEV_1$ is within 80% of the pre procedure value and patient is feeling well
    - Verify patient has gag reflex and is able to take liquids
    - Remind patient to take prophylactic prednisone or equivalent the day following bronchoscopy
    - Caution patient about the potential adverse events that they might experience including hemoptysis, fever, cough, and worsening of asthma symptoms. Patients should be advised to consult their physician if they experience any of these adverse events, or asthma symptoms that are not controlled by their reliever medications.
    - Contact patient via phone calls at 1, 2 and 7 days to assess post procedure status
    - Office visit at 2 to 3 weeks to assess clinical stability and schedule subsequent bronchial thermoplasty procedures as appropriate

## HOW SUPPLIED

The Alair® Bronchial Thermoplasty System Catheter Model ATS 2-5 is supplied sterile and is for SINGLE USE ONLY. **Do not re-sterilize or reuse** the Catheter, as this may result in patient harm or injury, transmittal of infectious disease, or product malfunction.

## MAINTENANCE AND TROUBLESHOOTING

- If mucus builds up in the airways and obscures visualization, remove the Catheter from the bronchoscope, provide irrigation with sterile saline, and suction the resulting fluid from the airways.
- If the electrode array does not expand or relax properly, remove the Catheter from the bronchoscope and squeeze and relax the Catheter handle to visually confirm that the electrode array is functioning properly. If it is not functioning properly, replace the Catheter and continue with the bronchial thermoplasty procedure.
- If you are alerted to auditory or visual cues from the Controller, consult the Alair® Bronchial Thermoplasty RF Controller Model ATS 200 Operator's Manual for operating and troubleshooting guidelines for the Controller.

## CUSTOMER SERVICE

All questions or concerns related to the Catheter should be directed to Asthmatx Customer Service or an authorized Asthmatx representative. No product may be returned without prior authorization. Please contact Asthmatx Customer Service or an authorized Asthmatx representative for a Return Material Authorization (RMA) number. See **"Contact Us"**.

## PRODUCT WARRANTIES

Asthmatx warrants until the expiration date marked on each Product (the "Warranty Period"), the Alair® Catheter sold hereunder will be free from material defects in materials, function and workmanship and will conform to Asthmatx's specifications in effect as of the date of manufacture. This limited warranty extends only to Customer as original purchaser unless otherwise agreed upon in writing by Asthmatx.

If during the Warranty Period: (i) Asthmatx is notified promptly upon discovery of any defect in the Alair® Catheter (ii) such Alair® Catheter is returned, shipping charges prepaid, to Asthmatx's designated facility with the prior approval of Asthmatx with a valid RMA number, and (iii) Asthmatx's inspections and tests determine that the Alair® Catheter is indeed defective and the Alair® Catheter has not been subjected to any of the conditions set forth below under "Warranty Exclusions," then, as Customer's sole remedy and Asthmatx's sole obligation under the foregoing warranty, Asthmatx will, at Asthmatx's option, replace without charge the defective Alair® Catheter or provide exchange credit. Any Alair® Catheter that has been replaced under this warranty shall have warranty coverage until the expiration date marked on the replacement Alair® Catheter.

WARRANTY EXCLUSIONS

THE WARRANTY SET FORTH IN "PRODUCT WARRANTIES" SHALL NOT APPLY IF THE DEFECTIVE ALAIR® CATHETER (A) HAS BEEN SUBJECTED TO ABUSE, MISUSE, NEGLECT, NEGLIGENCE, ACCIDENT, IMPROPER TESTING, IMPROPER INSTALLATION, IMPROPER STORAGE, IMPROPER HANDLING OR USE CONTRARY TO ANY DOCUMENTATION OR INSTRUCTIONS ISSUED BY ASTHMATX, (B) HAS BEEN REPAIRED OR ALTERED, (C) HAS NOT BEEN INSTALLED, OPERATED, AND MAINTAINED IN ACCORDANCE WITH THE DOCUMENTATION OR OPERATED OUTSIDE OF THE ENVIRONMENTAL SPECIFICATIONS FOR THE ALAIR® CATHETER; (D) HAS FAILED DUE TO AN ACT OF NATURE, INCLUDING BUT NOT LIMITED TO FIRE, FLOOD, TORNADO, EARTHQUAKE, HURRICANE OR LIGHTNING OR (E) HAS BEEN USED WITH ANY DEVICES, ACCESSORIES OR EQUIPMENT NOT MANUFACTURED BY OR APPROVED BY ASTHMATX FOR THE ALAIR® SYSTEM. IN ADDITION, THE FOREGOING WARRANTY SHALL NOT APPLY TO ALAIR® CATHETER(S) (A) MARKED OR IDENTIFIED AS "EVALUATION," OR "DEMONSTRATION" OR "NOT FOR HUMAN USE" OR (B) LOANED OR PROVIDED TO CUSTOMER AT NO COST.

DISCLAIMER OF WARRANTY

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## SYMBOL LEGEND

| | |
|---|---|
|  | Model Number |
|  | Caution: Consult Accompanying Documents |
|  | Radiation sterilized. Sterility guaranteed if package unopened or undamaged. |
|  | Lot Number |
|  | Manufacturer Name |
|  | Use by |
|  | For SINGLE-USE ONLY. |
|  | For sale or use by or on order of a physician only |

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PN 11678 Rev E
April 2010

# Appendix C

US006411852B1

(12) **United States Patent**
**Danek et al.**

(10) **Patent No.: US 6,411,852 B1**
(45) **Date of Patent: *Jun. 25, 2002**

(54) **MODIFICATION OF AIRWAYS BY APPLICATION OF ENERGY**

(75) Inventors: **Christopher J. Danek**, Palo Alto; **Thomas M. Keast**, San Jose; **Bryan E. Loomas**, Saratoga, all of CA (US)

(73) Assignee: **Broncus Technologies, Inc.**, Mountain View, CA (US)

( * ) Notice: This patent issued on a continued prosecution application filed under 37 CFR 1.53(d), and is subject to the twenty year patent term provisions of 35 U.S.C. 154(a)(2).

Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/296,040**

(22) Filed: **Apr. 21, 1999**

**Related U.S. Application Data**

(63) Continuation-in-part of application No. 09/095,323, filed on Jun. 10, 1998.

(51) **Int. Cl.**[7] ..... **A61F 7/12**

(52) **U.S. Cl.** ..... **607/42**; 607/89; 607/101; 607/96; 606/2; 606/14; 606/28; 606/41; 606/48; 606/50; 128/898

(58) **Field of Search** ..... 607/88–94, 96, 607/98, 42, 101, 113; 128/898; 606/41, 48, 50

(56) **References Cited**

U.S. PATENT DOCUMENTS

| | | | |
|---|---|---|---|
| 1,155,169 | A | 9/1915 | Starkweather |
| 1,207,479 | A | 12/1916 | Bisgaard |
| 2,072,346 | A | 3/1937 | Smith |
| 3,568,659 | A | 3/1971 | Karnegis |
| 3,692,029 | A | 9/1972 | Adair |
| 4,522,212 | A | 6/1985 | Gelinas et al. |

(List continued on next page.)

FOREIGN PATENT DOCUMENTS

| | | | |
|---|---|---|---|
| EP | 0 908 150 | A1 | 4/1999 |
| FR | 2659240 | | 9/1991 |
| WO | WO 98/44854 | A1 | 10/1998 |
| WO | WO 98/56324 | A1 | 12/1998 |
| WO | WO 98/58681 | A2 | 12/1998 |
| WO | WO 99/03413 | A1 | 1/1999 |
| WO | WO 99/13779 | A2 | 3/1999 |
| WO | WO 99/13779 | A3 | 3/1999 |
| WO | WO 99/34741 | A1 | 7/1999 |
| WO | WO 99/44506 | A1 | 9/1999 |
| WO | WO 99/45855 | A1 | 9/1999 |
| WO | WO 00/51510 | A1 | 9/2000 |
| WO | WO 01/03642 | A1 | 1/2001 |

OTHER PUBLICATIONS

Wiggs et al., "On the mechanism of mucosal folding in normal asthmatic airways", The American Physiological Society, 0161–7569/97, 1997.*

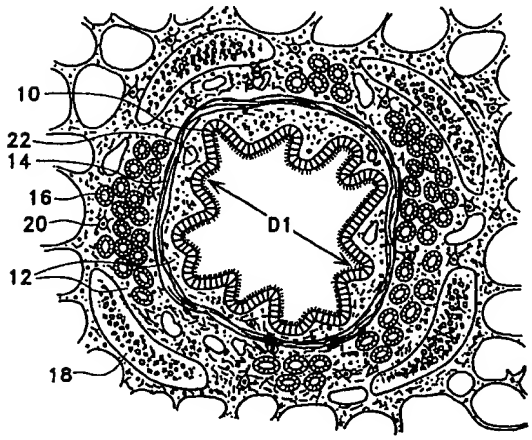
(List continued on next page.)

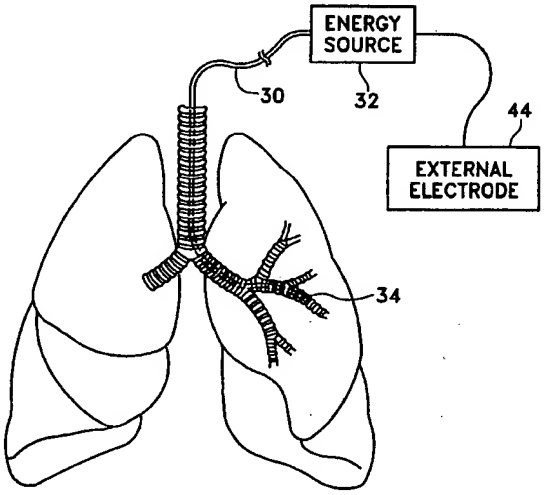
*Primary Examiner*—Linda C. M. Dvorak
*Assistant Examiner*—A. Farah
(74) *Attorney, Agent, or Firm*—Morrison & Foerster LLP

(57) **ABSTRACT**

A method for decreasing responsiveness or decreasing resistance to airflow of airways involves the transfer of energy to or from the airway walls to prevent or reduce airway constriction and other symptoms of lung diseases. The treatment reduces the ability of the airways to contract during an acute narrowing of the airways, reduces mucus plugging of the airways, and/or increases the airway diameter. The method provides a longer duration and/or more effective treatment for lung diseases than currently used drug treatments, and obviate patient compliance issues.

**54 Claims, 10 Drawing Sheets**



U.S. PATENT DOCUMENTS


| | | | | | |
|---|---|---|---|---|---|
| 4,565,200 | A | | 1/1986 | Cosman | |
| 4,584,998 | A | | 4/1986 | McGrail | |
| 4,612,934 | A | * | 9/1986 | Borkan | 128/421 |
| 4,674,497 | A | | 6/1987 | Ogasawara | |
| 4,706,688 | A | | 11/1987 | Michael et al. | |
| 4,709,698 | A | | 12/1987 | Johnston et al. | |
| 4,802,492 | A | | 2/1989 | Grunstein | |
| 4,827,935 | A | * | 5/1989 | Geddes et al. | 128/419 |
| 4,862,886 | A | | 9/1989 | Clarke et al. | |
| 4,920,978 | A | | 5/1990 | Colvin | |
| 4,955,377 | A | | 9/1990 | Lennox et al. | |
| 4,976,709 | A | | 12/1990 | Sand | |
| 5,019,075 | A | | 5/1991 | Spears et al. | |
| 5,053,033 | A | | 10/1991 | Clarke | |
| 5,056,519 | A | * | 10/1991 | Vince | 128/419 |
| 5,084,044 | A | | 1/1992 | Quint | |
| 5,096,916 | A | | 3/1992 | Skupin | |
| 5,100,388 | A | | 3/1992 | Behl et al. | |
| 5,100,423 | A | | 3/1992 | Fearnot | |
| 5,103,804 | A | | 4/1992 | Abele et al. | |
| 5,116,864 | A | | 5/1992 | March et al. | |
| 5,117,828 | A | | 6/1992 | Metzger et al. | |
| 5,135,517 | A | | 8/1992 | McCoy | |
| 5,170,803 | A | | 12/1992 | Hewson et al. | |
| 5,174,288 | A | | 12/1992 | Bardy et al. | |
| 5,191,883 | A | | 3/1993 | Lennox et al. | |
| 5,255,678 | A | | 10/1993 | Deslauriers et al. | |
| 5,255,679 | A | | 10/1993 | Imran | |
| 5,265,604 | A | * | 11/1993 | Vince | 607/42 |
| 5,281,218 | A | | 1/1994 | Imran | |
| 5,293,869 | A | | 3/1994 | Edwards et al. | |
| 5,309,910 | A | | 5/1994 | Edwards et al. | |
| 5,313,943 | A | | 5/1994 | Houser et al. | |
| 5,345,936 | A | | 9/1994 | Pomeranz et al. | |
| 5,368,591 | A | | 11/1994 | Lennox et al. | |
| 5,370,679 | A | | 12/1994 | Atlee, III | |
| 5,374,287 | A | | 12/1994 | Rubin | |
| 5,383,917 | A | | 1/1995 | Desai et al. | |
| 5,394,880 | A | | 3/1995 | Atlee, III | |
| 5,396,887 | A | | 3/1995 | Imran | |
| 5,400,783 | A | | 3/1995 | Pomeranz et al. | |
| 5,411,025 | A | | 5/1995 | Webster, Jr. | |
| 5,415,166 | A | | 5/1995 | Imran | |
| 5,415,656 | A | | 5/1995 | Tihon et al. | |
| 5,417,687 | A | | 5/1995 | Nardella et al. | |
| 5,423,744 | A | | 6/1995 | Gencheff et al. | |
| 5,423,811 | A | | 6/1995 | Imran et al. | |
| 5,431,696 | A | | 7/1995 | Atlee, III | |
| 5,433,730 | A | | 7/1995 | Alt | |
| 5,443,470 | A | | 8/1995 | Stern et al. | |
| 5,454,782 | A | | 10/1995 | Perkins | |
| 5,456,667 | A | | 10/1995 | Ham et al. | |
| 5,458,596 | A | | 10/1995 | Lax et al. | |
| 5,465,717 | A | | 11/1995 | Imran et al. | |
| 5,471,982 | A | | 12/1995 | Edwards et al. | |
| 5,496,311 | A | | 3/1996 | Abele et al. | |
| 5,500,011 | A | | 3/1996 | Desai | |
| 5,505,728 | A | * | 4/1996 | Ellman et al. | 606/39 |
| 5,509,419 | A | | 4/1996 | Edwards et al. | |
| 5,522,862 | A | | 6/1996 | Testerman et al. | |
| 5,531,779 | A | | 7/1996 | Dahl et al. | |
| 5,545,161 | A | | 8/1996 | Imran | |
| 5,545,193 | A | | 8/1996 | Fleischman et al. | |
| 5,549,559 | A | | 8/1996 | Eshel | |
| 5,549,655 | A | * | 8/1996 | Erickson | 607/42 |
| 5,558,073 | A | | 9/1996 | Pomeranz et al. | |
| 5,562,608 | A | | 10/1996 | Sekins et al. | |
| 5,588,432 | A | | 12/1996 | Crowley | |
| 5,595,183 | A | | 1/1997 | Swanson et al. | |
| 5,598,848 | A | | 2/1997 | Swanson et al. | |
| 5,601,088 | A | | 2/1997 | Swanson et al. | |
| 5,605,157 | A | | 2/1997 | Panescu et al. | |
| 5,607,419 | A | | 3/1997 | Amplatz et al. | |
| 5,607,462 | A | | 3/1997 | Imran | |
| 5,620,438 | A | | 4/1997 | Amplatz et al. | |
| 5,624,439 | A | * | 4/1997 | Edwards et al. | 606/45 |
| 5,626,618 | A | | 5/1997 | Ward et al. | |
| 5,630,425 | A | | 5/1997 | Panescu et al. | |
| 5,634,471 | A | * | 6/1997 | Fairfax et al. | 128/725 |
| 5,678,535 | A | * | 10/1997 | DiMarco | 128/200.24 |
| 5,680,860 | A | | 10/1997 | Imran | |
| 5,681,308 | A | | 10/1997 | Edwards et al. | |
| 5,693,078 | A | | 12/1997 | Desai et al. | |
| 5,699,799 | A | * | 12/1997 | Xu et al. | 128/653.1 |
| 5,707,352 | A | | 1/1998 | Sekins et al. | |
| 5,722,401 | A | | 3/1998 | Pietroski et al. | |
| 5,722,403 | A | | 3/1998 | McGee et al. | |
| 5,722,416 | A | | 3/1998 | Swanson et al. | |
| 5,730,128 | A | | 3/1998 | Pomeranz et al. | |
| 5,730,726 | A | | 3/1998 | Klingenstein | |
| 5,730,741 | A | | 3/1998 | Horzewski et al. | |
| 5,740,808 | A | | 4/1998 | Panescu et al. | |
| 5,752,518 | A | | 5/1998 | McGee et al. | |
| 5,755,753 | A | | 5/1998 | Knowlton | |
| 5,759,158 | A | | 6/1998 | Swanson | |
| 5,769,846 | A | | 6/1998 | Edwards et al. | |
| 5,772,590 | A | | 6/1998 | Webster, Jr. | |
| 5,779,698 | A | | 7/1998 | Clayman et al. | |
| 5,782,239 | A | | 7/1998 | Webster, Jr. | |
| 5,782,899 | A | | 7/1998 | Imran | |
| 5,792,064 | A | | 8/1998 | Panescu et al. | |
| 5,795,303 | A | | 8/1998 | Swanson et al. | |
| 5,807,306 | A | | 9/1998 | Shapland et al. | |
| 5,810,807 | A | | 9/1998 | Ganz et al. | |
| 5,827,277 | A | | 10/1998 | Edwards | |
| 5,836,947 | A | | 11/1998 | Fleischman et al. | |
| 5,843,075 | A | | 12/1998 | Taylor | |
| 5,846,238 | A | | 12/1998 | Jackson et al. | |
| 5,848,969 | A | | 12/1998 | Panescu et al. | |
| 5,848,972 | A | | 12/1998 | Triedman et al. | |
| 5,855,577 | A | | 1/1999 | Murphy-Chutorian et al. | |
| 5,860,974 | A | | 1/1999 | Abele | |
| 5,863,291 | A | | 1/1999 | Schaer | |
| 5,865,791 | A | | 2/1999 | Whayne et al. | |
| 5,868,740 | A | | 2/1999 | LeVeen et al. | |
| 5,871,443 | A | | 2/1999 | Edwards et al. | |
| 5,871,523 | A | | 2/1999 | Fleischman et al. | |
| 5,873,865 | A | | 2/1999 | Horzewski et al. | |
| 5,881,727 | A | | 3/1999 | Edwards | |
| 5,882,346 | A | | 3/1999 | Pomeranz et al. | |
| 5,891,136 | A | | 4/1999 | McGee et al. | |
| 5,897,554 | A | | 4/1999 | Chia et al. | |
| 5,904,651 | A | | 5/1999 | Swanson et al. | |
| 5,904,711 | A | | 5/1999 | Flom et al. | |
| 5,908,445 | A | | 6/1999 | Whayne et al. | |
| 5,908,446 | A | | 6/1999 | Imran | |
| 5,911,218 | A | * | 6/1999 | DiMarco | 128/200.24 |
| 5,935,079 | A | | 8/1999 | Swanson et al. | |
| 5,941,869 | A | | 8/1999 | Patterson et al. | |
| 5,954,661 | A | | 9/1999 | Greenspon et al. | |
| 5,954,662 | A | | 9/1999 | Swanson et al. | |
| 5,964,753 | A | | 10/1999 | Edwards | |
| 5,964,796 | A | | 10/1999 | Imran | |
| 5,971,983 | A | | 10/1999 | Lesh | |
| 5,972,026 | A | * | 10/1999 | Laufer et al. | 607/96 |
| 5,979,456 | A | * | 11/1999 | Magovern | 128/899 |
| 5,991,650 | A | | 11/1999 | Swanson et al. | |
| 5,992,419 | A | | 11/1999 | Sterzer et al. | |
| 5,993,462 | A | | 11/1999 | Pomeranz et al. | |
| 5,999,855 | A | | 12/1999 | DiMarco | |
| 6,004,269 | A | | 12/1999 | Crowley et al. | |

| | | | | |
|---|---|---|---|---|
| 6,009,877 | A | | 1/2000 | Edwards |
| 6,024,740 | A | | 2/2000 | Lesh et al. |
| 6,036,687 | A | | 3/2000 | Laufer et al. |
| 6,053,172 | A | * | 4/2000 | Hovda et al. ..... 128/898 |
| 6,083,255 | A | | 7/2000 | Laufer et al. |
| 6,142,993 | A | | 11/2000 | Whayne et al. |
| 6,200,333 | B1 | | 3/2001 | Laufer |
| 6,254,598 | B1 | | 7/2001 | Edwards et al. |

OTHER PUBLICATIONS

U.S. application No. 09/176,899, Laufer, filed Oct. 22, 1998.

U.S. application No. 09/244,173, Laufer et al., filed Feb. 4, 1999.

U.S. application No. 09/280,672, Laufer et al., filed Mar. 29, 1999.

Barry R. Wiggs, et al., "On the Mechanism of Mucosal Folding in Normal and Asthmatic Airways," The American Physiological Society (1997) pp. 18141821.

Simon R. Johnson, et al. "*Synthetic Functions of Airway Smooth Muscle in Asthma*," Review.

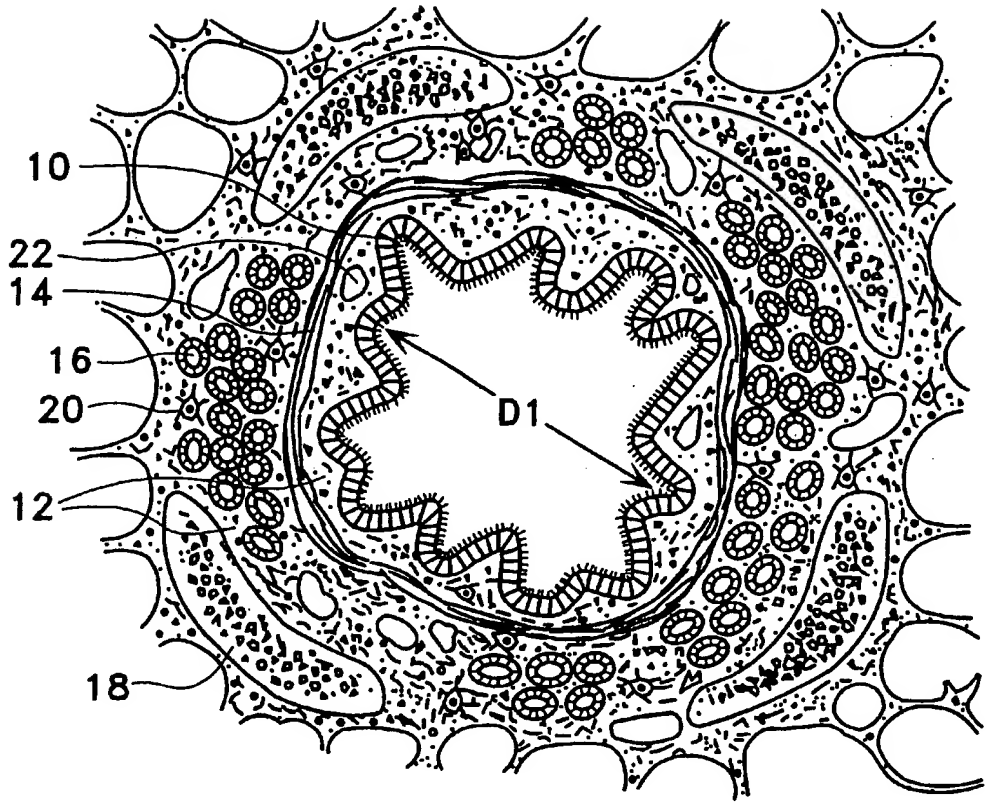
P.T. Macklem, "*Mechanical Factors Determining Maximum Bronchoconstriction*," European Respiratory Journal, Supplemental 6 (1989) pp. 516s–519s.

James C. Hogg, "*The Pathology of Asthma*," APMIS, No. 105 (1997) pp. 735–745.

Dierkesmann et al. (1990). "Indication and Results of Endobronchial Laser Therapy," *Lung* (Suppl.):1095–1102.

Netter, F.H. (1979). "Respiratory System: A Compilation of Paintings Depicting Anatomy and Embryology, Physiology, Pathology, Pathophysiology, and Clinical Features and Treatment of Diseases," vol. 7 *In The CIBA Collection of Medical Illustrations*. M.B. Divertie, ed., Summit: New Jersey, pp. 119–135.

* cited by examiner

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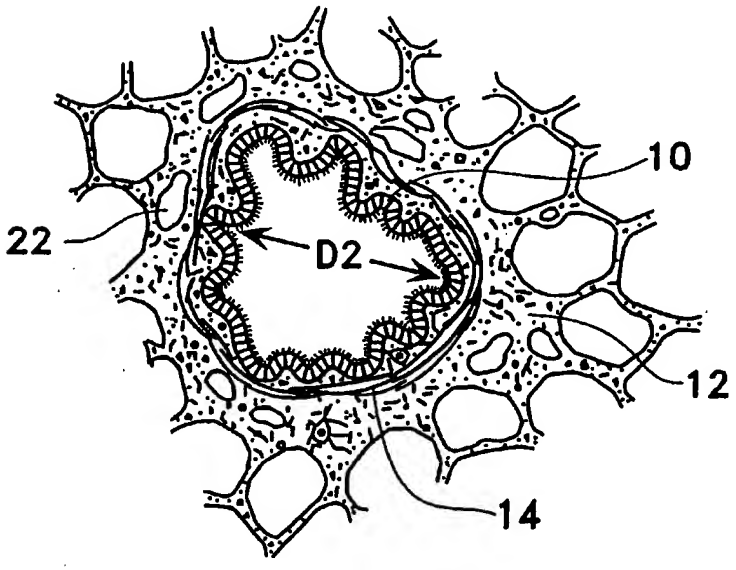


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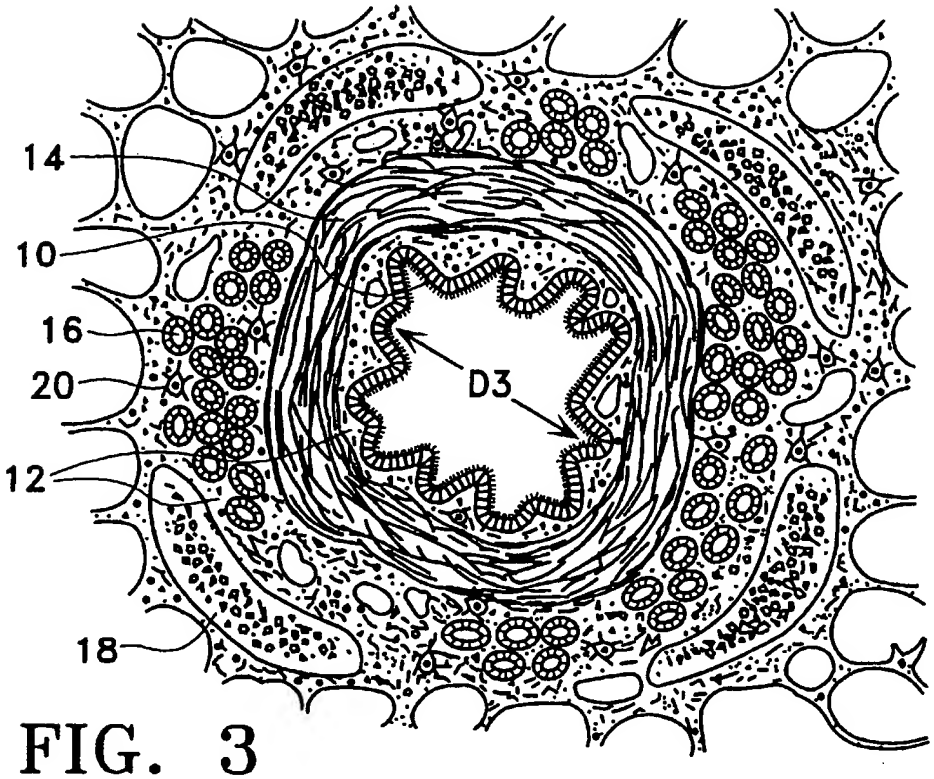
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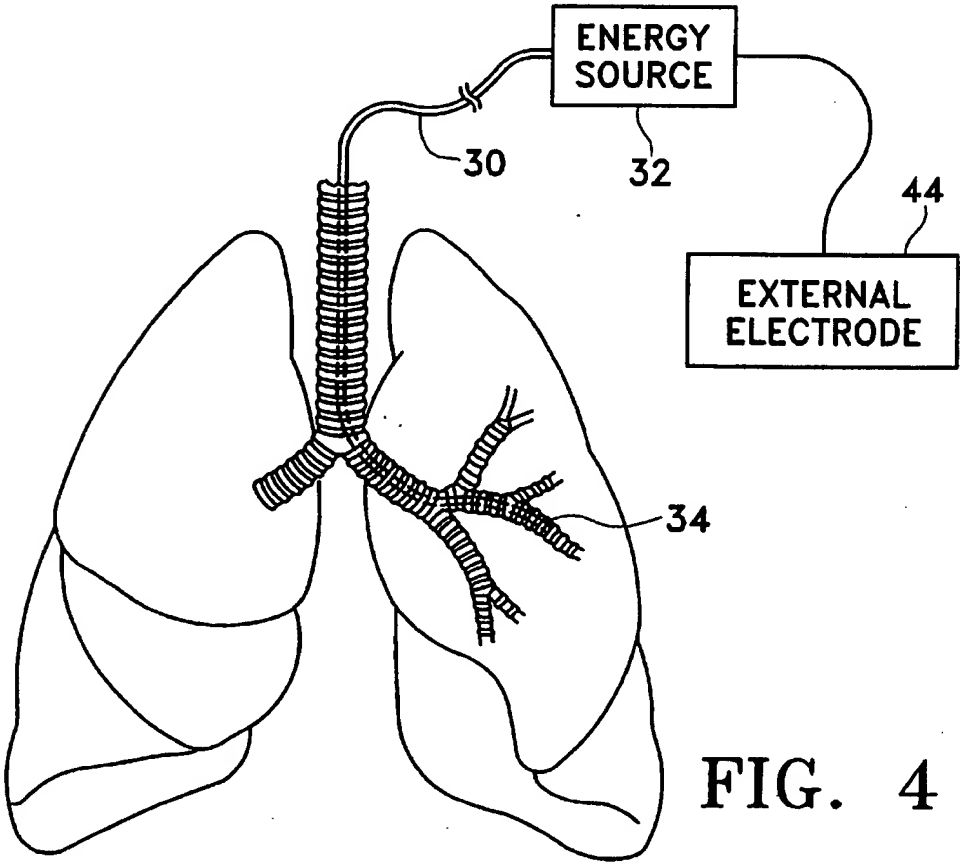
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EXTERNAL ELECTRODE
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FIG. 4

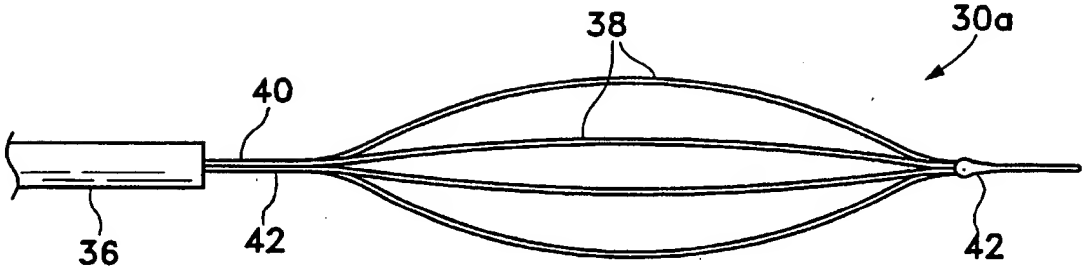
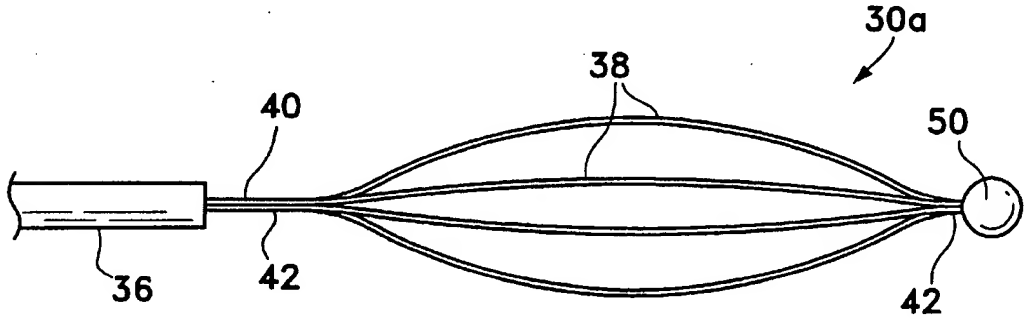



FIG. 5A

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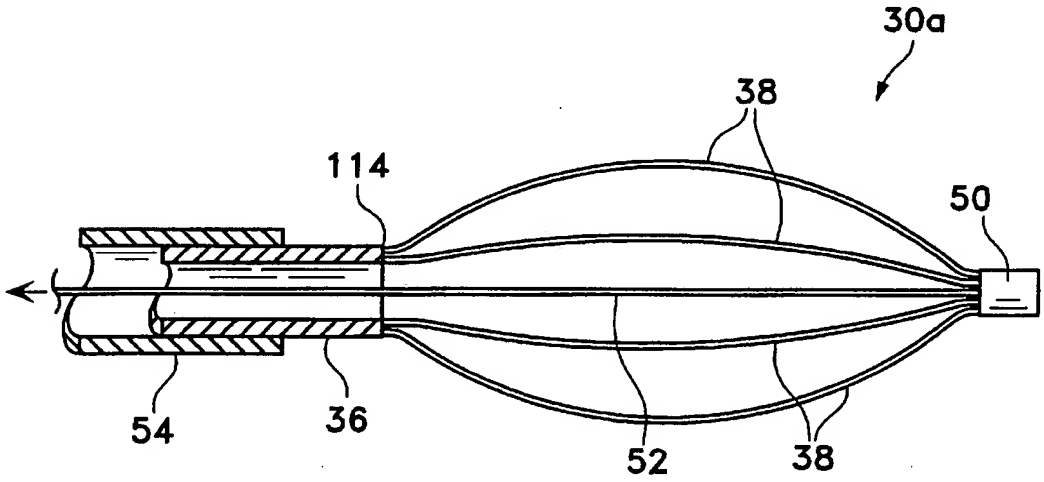


FIG. 5C

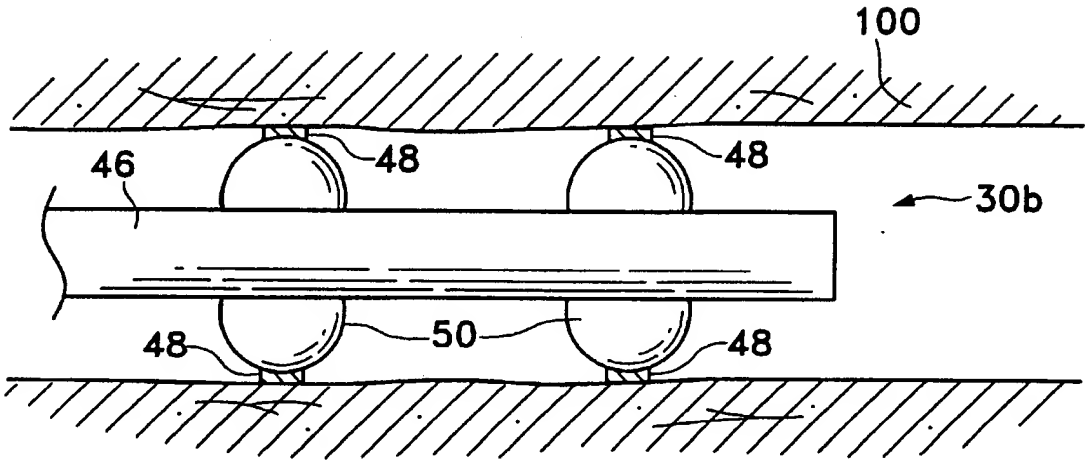


FIG. 6

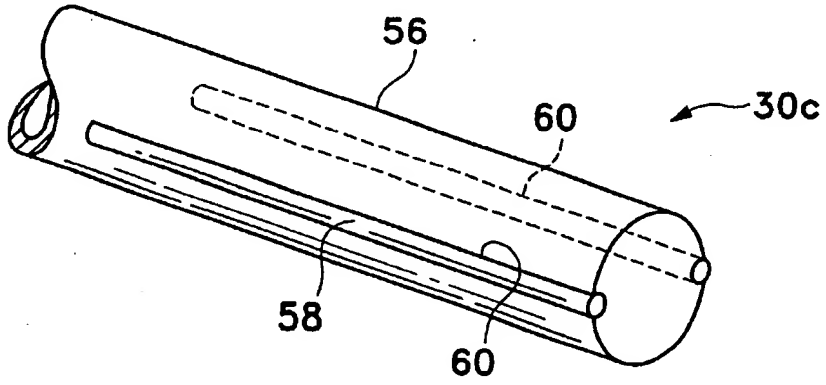


FIG. 7

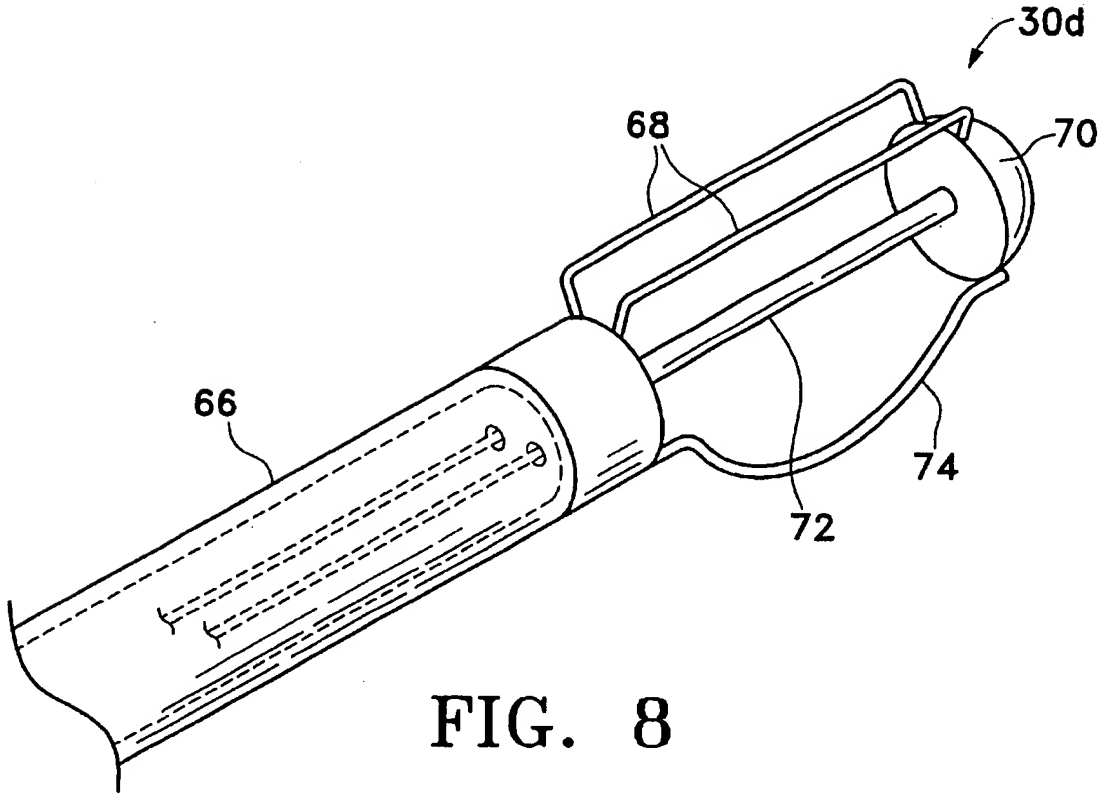


FIG. 8

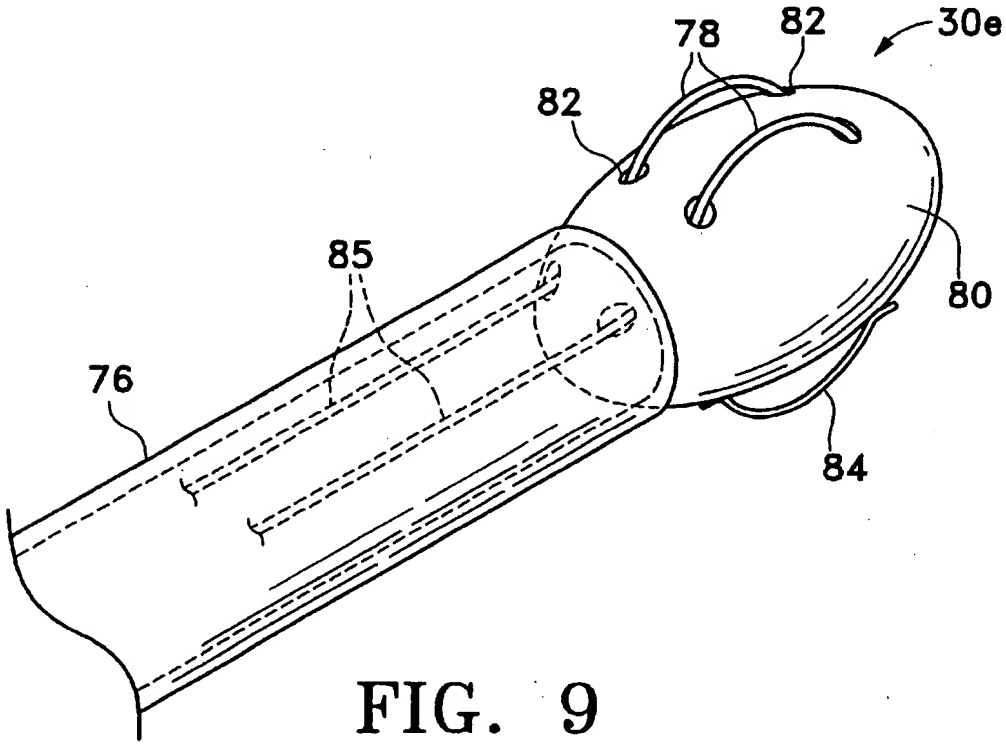


FIG. 9

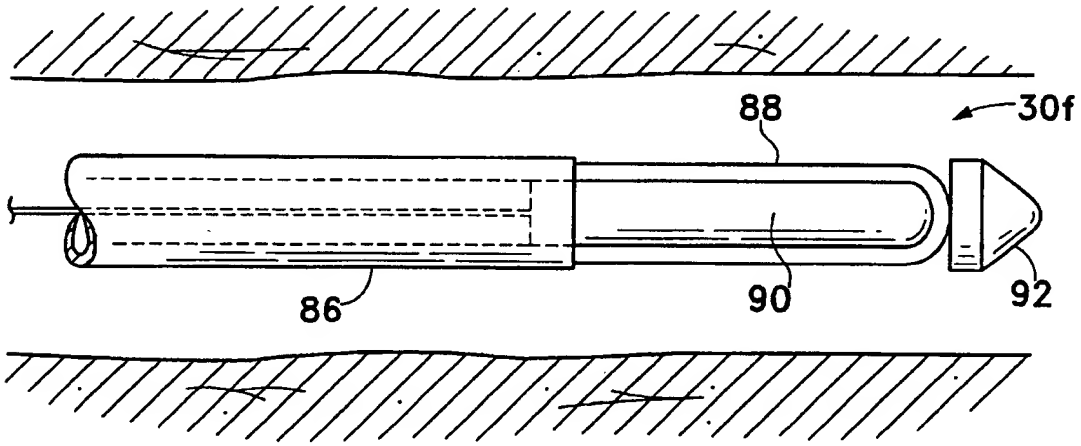


FIG. 10

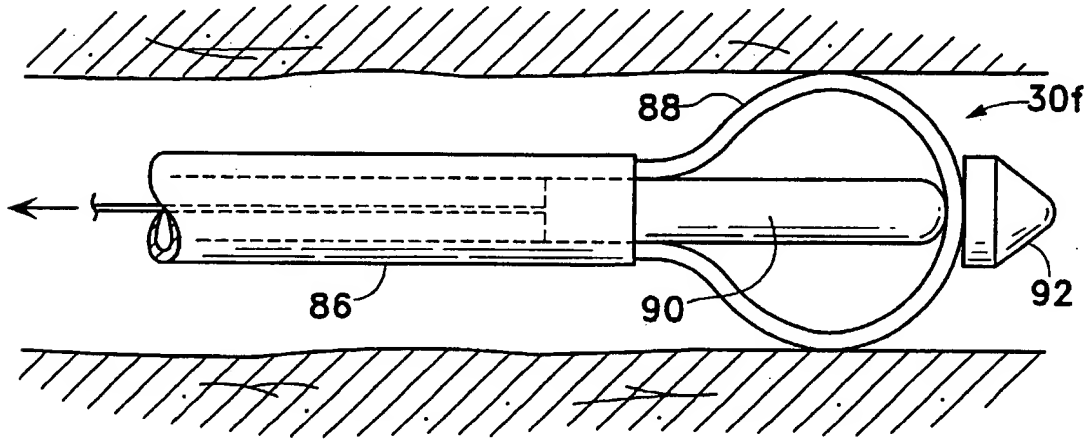


FIG. 11

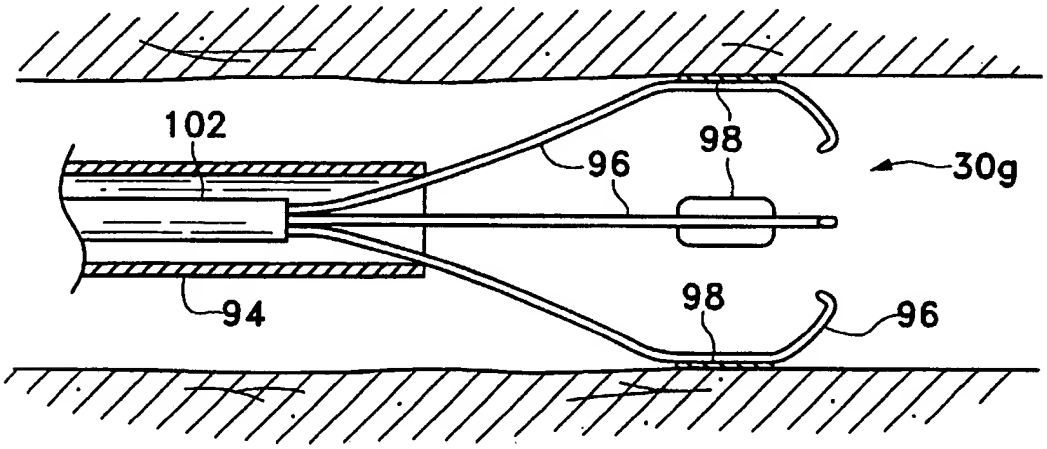


FIG. 12

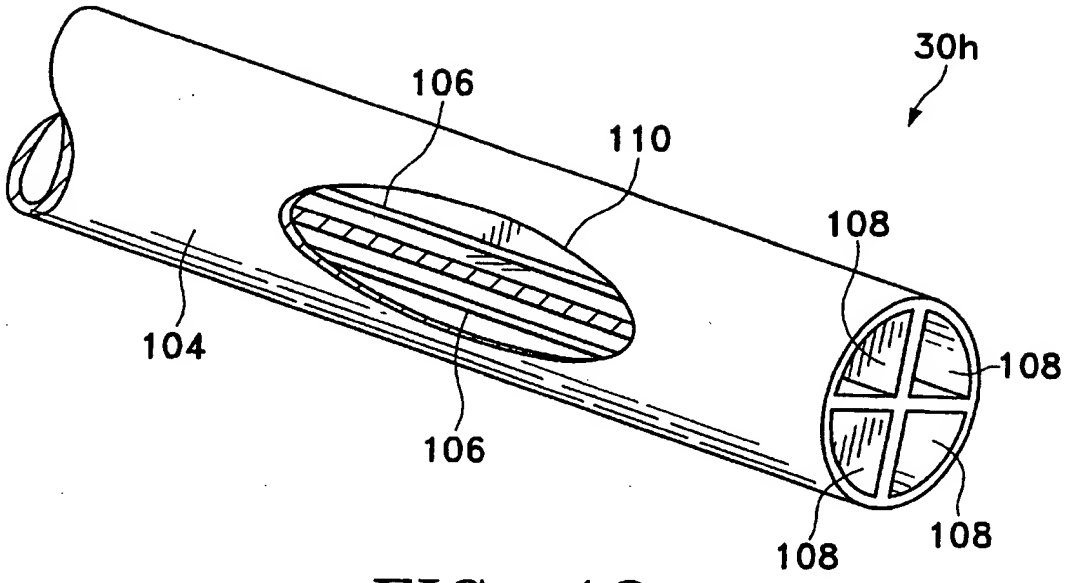


FIG. 13

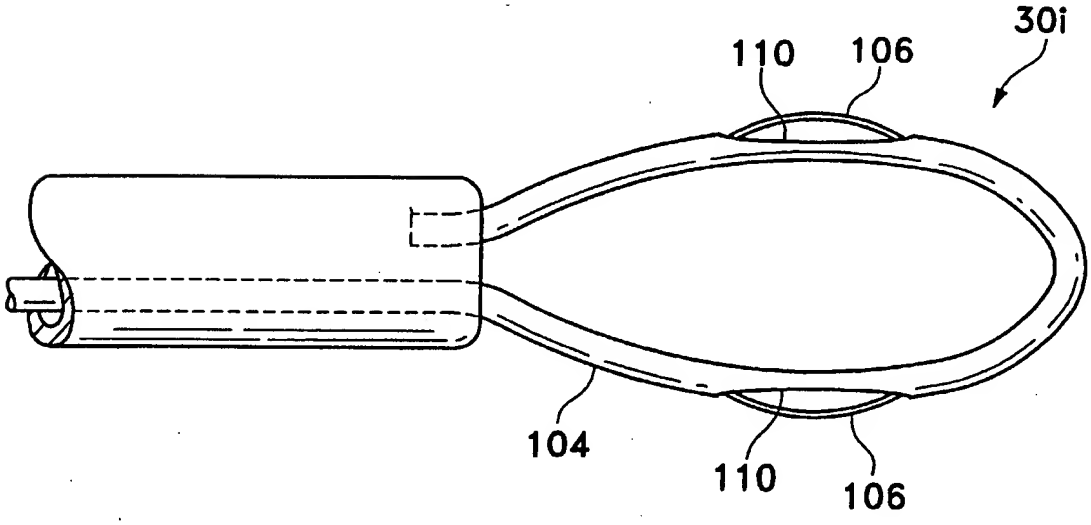


FIG. 14

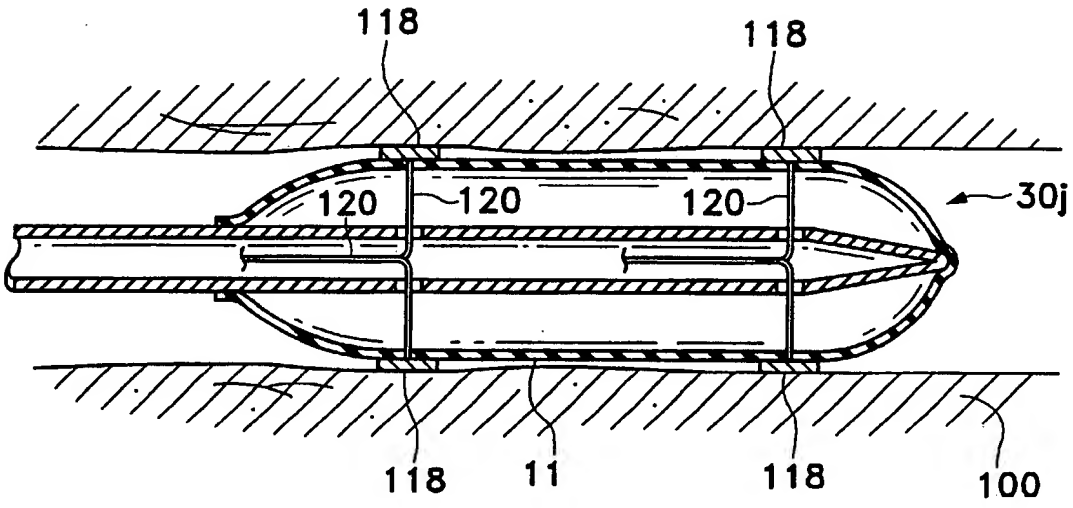


FIG. 15

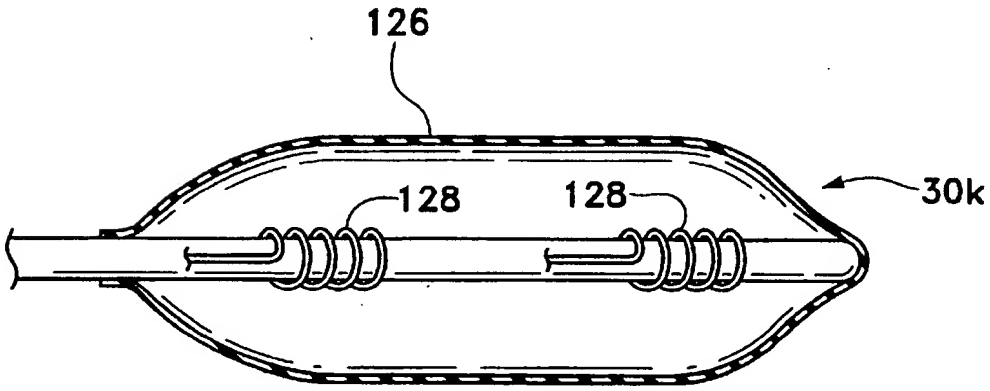


FIG. 16

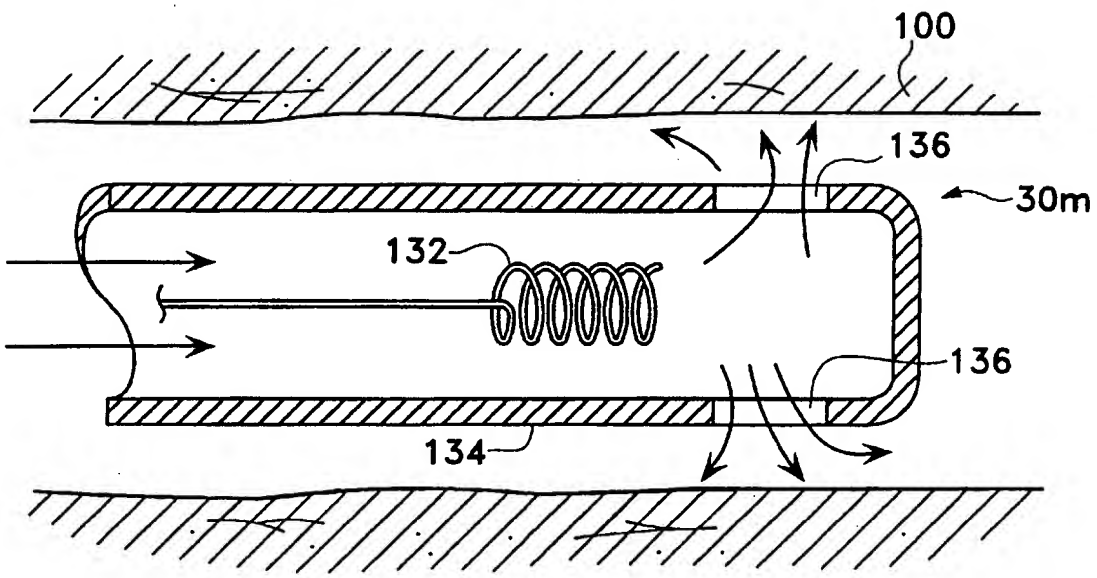


FIG. 17

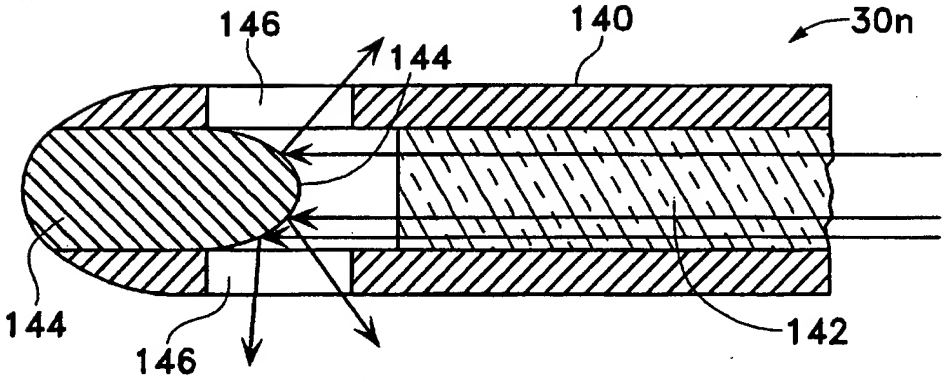


FIG. 18

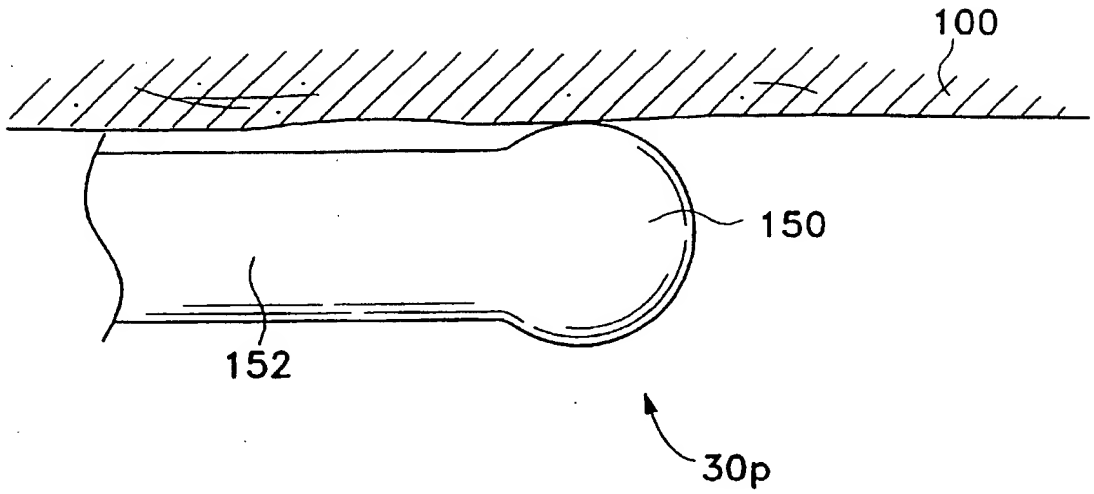


FIG. 19

# MODIFICATION OF AIRWAYS BY APPLICATION OF ENERGY

This is a Continuation-in-part application of U.S. application Ser. No. 09/095,323 filed Jun. 10, 1998, which is incorporated herein by reference in its entirety.

## BACKGROUND OF THE INVENTION

1. Field of the Invention

The invention relates to a method for treating lung disease, and more particularly, the invention relates to a method for treating the lungs by applying energy to the airways to reduce the ability of the airways to constrict or to reduce the resistance to airflow through the airways.

2. Brief Description of the Related Art

Asthma is a disease in which (1) bronchoconstriction, (2) excessive mucus production, and (3) inflammation and swelling of airways occur, causing widespread but variable airflow obstruction thereby making it difficult for the asthma sufferer to breath. Asthma is a chronic disorder, primarily characterized by persistent airway inflammation. However, asthma is further characterized by acute episodes of additional airway narrowing via constriction of hyperresponsive airway smooth muscle.

Asthma stimuli may be allergenic or non-allergenic. Examples of allergenic stimuli include pollen, pet dander, dust mites, bacterial or viral infection, mold, dust, or airborne pollutants; non-allergenic stimuli include exercise or exposure to cold, dry air.

In asthma, chronic inflammatory processes in the airway play a central role. Many cells and cellular elements are involved in the inflammatory process, particularly mast cells, eosinophils T lymphocytes, neutrophils, epithelial cells, and even airway smooth muscle itself. The reactions of these cells result in an associated increase in the existing sensitivity and hyperresponsiveness of the airway smooth muscle cells that line the airways to the particular stimuli involved.

The chronic nature of asthma can also lead to remodeling of the airway wall (i.e., structural changes such as thickening or edema) which can further affect the function of the airway wall and influence airway hyperresponsiveness. Other physiologic changes associated with asthma include excess mucus production, and if the asthma is severe, mucus plugging, as well as ongoing epithelial denudation and repair. Epithelial denudation exposes the underlying tissue to substances that would not normally come in contact with them, further reinforcing the cycle of cellular damage and inflammatory response.

In susceptible individuals, asthma symptoms include recurrent episodes of shortness of breath (dyspnea), wheezing, chest tightness, and cough. Currently, asthma is managed by a combination of stimulus avoidance and pharmacology.

Stimulus avoidance is accomplished via systematic identification and minimization of contact with each type of stimuli. It may, however, be impractical and not always helpful to avoid all potential stimuli.

Asthma is managed pharmacologically by: (1) long term control through use of anti-inflammatories and long-acting bronchodilators and (2) short term management of acute exacerbations through use of short-acting bronchodilators. Both approaches require repeated and regular use of the prescribed drugs. High doses of corticosteroid anti-inflammatory drugs can have serious side effects that require careful management. In addition, some patients are resistant to steroid treatment. Patient compliance with pharmacologic management and stimulus avoidance is often a barrier to successful asthma management.



Asthma is a serious disease with growing numbers of suffers. Current management techniques are neither completely successful nor free from side effects.

Accordingly, it would be desirable to provide an asthma treatment which improves airflow without the need for patient compliance.

In addition to the airways of the lungs, other body conduits such as the esophagus, ureter, urethra, and coronary arteries, are also subject to periodic spasms which cause hypertrophy and hyperplasia of the smooth muscle around these body conduits reducing the inner diameter of the conduits.

## SUMMARY OF THE INVENTION

The present invention relates to a method for treating bodily conduits by transfer of energy to or from the conduit walls to prevent the conduit from being able to constrict, to enlarge the conduit, or to reduce resistance to flow through the conduit. The invention is particularly directed to the treatment of the airways in the lungs to reduce the effects of asthma and other lung disease.

The present invention provides methods to decrease airway responsiveness and airway resistance to flow which may augment or replace current management techniques.

In accordance with one aspect of the present invention, a method for treating conditions of the lungs by decreasing airway responsiveness includes transferring energy to or from an airway wall to alter the airway wall in such a manner that the responsiveness of the airway is reduced.

In accordance with an additional aspect of the present invention, the energy transferred to or from the airway wall alters the structure of the airway wall.

In accordance with a further aspect of the present invention, the energy transferred to or from the airway wall alters the function of the airway wall.

In accordance with another aspect of the present invention, a method for treating conditions of the lungs by decreasing airway resistance to airflow includes transferring energy to or from an airway wall to alter the airway wall in such a manner that a resistance to airflow of the airway is decreased.

The present invention provides advantages of a treatment for asthma or other constriction or spasm of a bodily conduit by application of energy. The treatment reduces the ability of the airway to contract, reduces plugging of the airway, and/or increases the inner airway diameter.

## BRIEF DESCRIPTION OF THE DRAWINGS

The invention will now be described in greater detail with reference to the preferred embodiments illustrated in the accompanying drawings, in which like elements bear like reference numerals, and wherein:

FIG. **1** is a cross sectional view of a medium sized bronchus in a healthy patient;

FIG. **2** is a cross sectional view of a bronchiole in a healthy patient;

FIG. **3** is a cross sectional view of the bronchus of FIG. **1** showing the constriction occurring in an asthma patient;

FIG. **4** is a schematic side view of the lungs being treated with a treatment device according to the present invention;

FIGS. 5A and 5B are side views of two variations of a first embodiment of a treatment device having a plurality of wire shaped electrodes;

FIG. 5C is a cross sectional side view of another variation of the first embodiment of a treatment device having a plurality of wire shaped electrodes;

FIG. 6 is a side view of a second embodiment of a treatment device with electrodes positioned on expandable balloons;

FIG. 7 is a perspective view of a third embodiment of a treatment device with electrodes positioned in grooves;

FIG. 8 is a perspective view of a fourth embodiment of a treatment device with electrodes and a biasing element;

FIG. 9 is a perspective view of a fifth embodiment of a treatment device with electrodes and a biasing element;

FIG. 10 is a side view of a sixth embodiment of a treatment device in an unexpanded position;

FIG. 11 is a side view of the treatment device of FIG. 10 in an expanded position;

FIG. 12 is a side view of a seventh embodiment of a treatment device in an expanded position;

FIG. 13 is a side view of an eighth embodiment of a treatment device having a plurality of lumens containing electrodes;

FIG. 14 is a side view of a ninth embodiment of a treatment device having electrodes exposed by cut away sections of a tube;

FIG. 15 is a side cross sectional view of a tenth embodiment of a treatment device with electrodes positioned on an expandable balloon;

FIG. 16 is a schematic side view of a eleventh embodiment of a treatment device with a balloon for heating of tissue;

FIG. 17 is a side cross sectional view of a twelfth embodiment of a treatment device for treatment with heated fluid;

FIG. 18 is a side cross sectional view of a thirteenth embodiment of a treatment device for treatment with radiation; and

FIG. 19. is a side view of a fourteenth embodiment of a treatment device for treatment with a cryoprobe.

## DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

FIGS. 1 and 2 illustrate cross sections of two different airways in a healthy patient. The airway of FIG. 1 is a medium sized bronchus having an airway diameter D1 of about 3 mm. FIG. 2 shows a section through a bronchiole having an airway diameter D2 of about 1.5 mm. Each airway includes a folded inner surface or epithelium 10 surrounded by stroma 12 and smooth muscle tissue 14. The larger airways including the bronchus shown in FIG. 1 also have mucous glands 16 and cartilage 18 surrounding the smooth muscle tissue 14. Nerve fibers 20 and blood vessels 22 also surround the airway.

FIG. 3 illustrates the bronchus of FIG. 1 in which the smooth muscle 14 has hypertrophied and increased in thickness causing the airway diameter to be reduced from the diameter D1 to a diameter D3.

There are several ways to decrease the resistance to airflow though the airways which occurs in asthma patients both at rest and during an asthma attack. One such treatment alters the structure of the airway, such as by reducing smooth muscle or other tissue. Another treatment alters the function of the airway, such as by reducing smooth muscle contraction, mucus gland secretions, or disrupting the inflammatory response. These treatments can be performed by applying energy of different types and in different patterns to achieve the desired results.

FIG. 4 is a schematic side view of the lungs being treated with a treatment device 30 according to the present invention. The treatment device 30 is an elongated member for delivery of energy from an energy source 32 to a treatment site 34 within the lungs. The energy may be delivered by the treatment device 30 in a variety of treatment patterns to achieve a desired response. Examples of patterns are discussed in further detail below. The energy which is delivered by the treatment device 30 may be any of a variety of types of energy including, but not limited to, radiant, laser, radio frequency, microwave, heat energy, or mechanical energy (such as in the form of cutting or mechanical dilation). In addition, the delivery of laser or light energy may be in conjunction with the delivery of a photodynamic agent, where the laser or light energy stimulates the photodynamic agent and initiates a cytotoxic, or cell damaging chemical reaction.

### Reducing the Ability of the Airway to Contract

The energy treatment of the airways may be used to reduce the ability of the airways to narrow or reduce in caliber as a result of airway smooth muscle contraction. This treatment to reduce the ability of the smooth muscle to contract provides the benefit of lessening the severity of an asthma attack. The reduction in the ability of smooth muscle to contract may be achieved by treating the smooth muscle itself or by treating other tissues which in turn influence smooth muscle contraction or the response of the airway to smooth muscle contraction. Treatment may also reduce airway responsiveness or the tendency of the airway to narrow or constrict in response to stimulus.

The amount of smooth muscle surrounding the airway can be reduced by exposing the smooth muscle to energy which either kills the smooth muscle cells or prevents the cells from replicating. The reduction in smooth muscle reduces the ability of the smooth muscle to contract and narrow the airway during a spasm. The reduction in smooth muscle has the added benefit of increasing the caliber of the airways, reducing the resistance to airflow through the airways. In addition to use in debulking enlarged smooth muscle tissue to open up the airways, the method of the present invention may also be used for eliminating smooth muscle altogether. The elimination of the smooth muscle tissue prevents the hyperreactive airways of an asthma patient from contracting or spasming, reducing or eliminating this asthma symptom.

The ability of the smooth muscle to contract can also be altered by treatment of the smooth muscle in particular patterns. The smooth muscle is arranged around the airways in a generally helical pattern with pitch angles ranging from about −30 to about +30 degrees. Thus, the treatment of the smooth muscle by energy which is selectively delivered in an appropriate pattern can interrupt or cut through the helical pattern at a proper frequency and prevent the smooth muscle from constricting. This procedure of patterned application of energy eliminates contraction of the airways without completely eradicating smooth muscle. A pattern for treatment can be chosen from a variety of patterns including longitudinal stripes, circumferential bands, helical stripes, and the like as well as spot patterns having rectangular, elliptical, circular or other shapes. The size, number, and spacing of the treatment bands, stripes, or spots are chosen to provide

a desired clinical effect of reduced airway responsiveness while limiting insult to the airway to a clinically acceptable level.

The patterned treatment of the tissues surrounding the airways with energy provides various advantages. The careful selection of the portion of the airway to be treated allows desired results to be achieved while the total healing load may be reduced. Patterned treatment can also achieve desired results with decreased morbidity, preservation of epithelium, and preservation of a continuous or near continuous ciliated inner surface of the airway for mucociliary clearance. The pattern of treatment may also be chosen to achieve desired results while limiting total treatment area and/or the number of airways treated, thereby improving speed and ease of treatment.

Application of energy to the smooth muscle surrounding the airways also may be used to cause the DNA of the smooth muscle cells to become cross linked. The treated smooth muscle cells with cross linked DNA are incapable of replicating. Accordingly, over time, as the smooth muscle cells die, the total thickness of smooth muscle decreases because of the inability of the cells to replicate. The programed cell death causing a reduction in the volume of tissue is called apoptosis. This treatment does not cause an immediate effect but causes shrinking of the smooth muscle and opening of the airway over time and substantially prevents regrowth. The application of energy to the walls of the airway also can be used to cause a cross linking of the DNA of the mucus gland cells preventing them from replicating and reducing excess mucus plugging or production over time.

The ability of the airways to contract can also be reduced by altering mechanical properties of the airway wall, such as by increasing stiffness of the wall or by increasing parenchymal tethering of the airway wall. Both of these methods provide increased forces which oppose contraction of the smooth muscle and narrowing of the airway.

There are several ways to increase the stiffness of the airway wall. One way to increase stiffness is to induce a fibrosis or wound healing response by causing trauma to the airway wall. The trauma can be caused by delivery of therapeutic energy to the tissue in the airway wall or by mechanical insult to the tissue. The energy is preferably delivered in such a way that it minimizes or limits the intra-luminal thickening that can occur.

Another way to increase the effective stiffness of the airway wall is by altering the submucosal folding of the airway upon narrowing. The submucosal layer is directly beneath the epithelium and its basement membrane and inside the airway smooth muscle. As an airway narrows, its perimeter remains relatively constant, with the mucosal layer folding upon itself. As the airway narrows further, the mucosal folds mechanically interfere with each other, effectively stiffening the airway. In asthmatic patients, the number of folds is fewer and the size of the folds is larger, and thus, the airway is free to narrow with less mechanical interference of mucosal folds than in a healthy patient. Thus, asthmatic patients have a decrease in stiffness of the airway and less resistance to narrowing.

The mucosal folding in asthmatic patients can be improved by treatment of the airway in a manner which encourages folding. Preferably, a treatment will increase the number of folds and/or decrease the size of the folds in the mucosal layer. For example, treatment of the airway wall in a pattern such as longitudinal stripes can encourage greater number of mucosal folds and increase airway stiffness.

The mucosal folding can also be increased by encouraging a greater number of smaller folds by reducing the thickness of the submucosal layer. The decreased thickness of the submucosal layer may be achieved by application of energy which either reduces the number of cells in the submucosal layer or which prevents replication of the cells in the submucosal layer. A thinner submucosal layer will have an increased tendency to fold and increased mechanical stiffening caused by the folds.

Another method for reducing the ability of the airways to contract is to improve parenchymal tethering. The parenchyma surrounds all airways and includes the alveolus and tissue connected to and surrounding the outer portion of the airway wall. The parenchyma includes the alveolus and tissue connected to and surrounding the cartilage that supports the larger airways. In a healthy patient, the parenchyma provides a tissue network which connects to and helps to support the airway. Edema or accumulation of fluid in lung tissue in asthmatic patients is believed to decouple the airway from the parenchyma reducing the restraining force of the parenchyma which opposes airway constriction. Application of therapeutic energy can be used to treat the parenchyma to reduce edema and/or improve parenchymal tethering.

In addition, energy can be used to improve connection between the airway smooth muscle and submucosal layer to the surrounding cartilage, and to encourage wound healing, collagen deposition, and/or fibrosis in the tissue surrounding the airway to help support the airway and prevent airway contraction.

### Increasing the Airway Diameter

Airway diameter in asthmatic patients is reduced due to hypertrophy of the smooth muscle, chronic inflammation of the airway tissues, and general thickening of all parts of the airway wall. The overall airway diameter can be increased by a variety of techniques to improve the passage of air through the airways. Application of energy to the airway smooth muscle of an asthmatic patient can be used to debulk or reduce the volume of smooth muscle. This reduced volume of smooth muscle increases the airway diameter for improved air exchange.

The airway diameter can also be increased by reducing inflammation and edema of the tissue surrounding the airway. Inflammation and edema (accumulation of fluid) of the airway occur in an asthmatic patient due to irritation. The inflammation and edema can be reduced by application of energy to stimulate wound healing and regenerate normal tissue. Healing of the epithelium or sections of the epithelium experiencing ongoing denudation and renewal allows regeneration of healthy epithelium with less associated airway inflammation. The less inflamed airway has an increased airway diameter both at a resting state and in constriction. The wound healing can also deposit collagen which improves parachymal tethering.

Inflammatory mediators released by tissue in the airway wall may serve as a stimulus for airway smooth muscle contraction. Smooth muscle contraction, inflammation, and edema can be reduced by a therapy which reduces the production and release of inflammatory mediators. Examples of inflammatory mediators are cytokines, chemokines, and histamine. The tissues which produce and release inflammatory mediators include airway smooth muscle, epithelium, and mast cells. Treatment of these structures with energy can reduce the ability of the airway structures to produce or release inflammatory mediators.

The reduction in released inflammatory mediators will reduce chronic inflammation, thereby increasing the airway inner diameter, and may also reduce contraction of airway smooth muscle.

A further method for increasing the airway diameter is by denervation. A resting tone of smooth muscle is nerve regulated by release of catecholamines. Thus, by damaging or eliminating nerve tissue in the airways the resting tone of the airway smooth muscle will be reduced, and the airway diameter will be increased.

Reducing Plugging of the Airway

Excess mucus production and mucus plugging are common problems during both acute asthma exasterbations and in chronic asthma management. Excess mucus in the airways increases the resistance to airflow through the airways by physically blocking all or part of the airway. Excess mucus may also contribute to increased numbers of leukocytes found in airways of asthmatic patients by trapping leukocytes. Thus, excess mucus can increase chronic inflammation of the airways.

One type of asthma therapy involves treatment of the airways with energy to target and reduce mucus producing cells and glands. The treatment can eliminate all or a portion of the mucus producing cells and glands, can prevent the cells from replicating or can inhibit their ability to secrete mucus. This treatment will have both chronic benefits in increasing airflow through the airways and will lessen the severity of acute exacerbations.

FIGS. **5–19** illustrate different treatment devices for transferring energy to or from the airways. These are just some of the examples of the type of treatment devices which may be used to perform the methods according to the present invention. It should be recognized that each of the treatment devices described below can be modified to deliver or remove energy in different patterns depending on the treatment to be performed. The treatment devices may be actuated continuously for a predetermined period while stationary, may be pulsed, may be actuated multiple times as they are moved along an airway, may be operated continuously while moving the device in an airway to achieve a "painting" of the airway, or may be actuated in a combination of any of these techniques. The particular energy application pattern desired can be achieved by configuring the treatment device itself or by moving the treatment device to different desired treatment locations in the airway.

The treatment of an airway with the treatment device may involve placing a visualization system such as an endoscope or bronchoscope into the airways. The treatment device is then inserted through or next to the bronchoscope or endoscope while visualizing the airways. Alternatively, it is possible to build the means for visualization directly into the treatment device using fiber optic imaging and lenses or a CCD and lens arranged at the distal portion of the treatment device. The treatment device may also be positioned using radiographic visualization such as fluoroscopy or other external visualization means. The treatment device which has been positioned with a distal end within an airway to be treated is energized so that energy is applied to the tissue of the airway walls in a desired pattern and intensity. The distal end of the treatment device may be moved through the airway in a uniform painting like motion to expose the entire length of an airway to be treated to the energy. The treatment device may be passed along the airway one or more times to achieve adequate treatment. The painting like motion used to exposed the entire length of an airway to the energy may be performed by moving the entire treatment device from the proximal end either manually or by motor. Alternatively, segments, stripes, rings or other treatment patterns may be used.

According to one embodiment of the invention, the energy is transferred to or from the opening region of an airway, preferably within a length of approximately two times the airway diameter or less, and to regions of airways distal to bifurcations and side branches, preferably within a distance of approximately twice the airway diameter or less. The invention may also be used to treat long segments of un-bifurcated airway.

The treatment devices of FIGS. **5–15** include tissue contacting electrodes configured to be placed within the airway. These devices can be used for delivering radio frequency in either a monopolar or a bipolar manner or for delivering other energy to the tissue, such as conducted heat energy from resistively heated electrodes. For monopolar energy delivery, one or more electrodes of the treatment device are connected to a single pole of the energy source **32** and an optional external electrode **44** is connected to an opposite pole of the energy source. For bipolar energy delivery, multiple electrodes are connected to opposite poles of the energy source **32** and the external electrode **44** is omitted. The number and arrangement of the electrodes may vary depending on the pattern of energy delivery desired. The treatment devices of FIGS. **16–18** are used to deliver radiant or heat energy to the airway. The treatment device of FIG. **16** can also deliver indirect radio frequency or microwave energy to the tissue. Finally the treatment device of FIG. **19** is used to remove heat energy from the tissue.

The treatment device **30***a* of FIG. **5**A includes a catheter **36** for delivering a shaft **40** having a plurality of electrodes **38** to a treatment site. The electrodes **38** are formed from a plurality of wires which are soldered or otherwise connected together at two connection areas **42**. The electrodes **38** between the connection areas **42** are formed into a basket shape so that arch shaped portions of the wires will contact the walls of an airway. The wires may be coated with an insulating material except at the tissue contact points. Alternatively, the wires of the basket may be exposed while the connection areas **42** and shaft **40** are insulated. Preferably, the electrodes **38** are formed of a resilient material which will allow the distal end of the treatment device to be retracted into the catheter **36** for delivery of the catheter to the treatment site and will allow the electrodes to return to their original basket shape upon deployment. The treatment device **30***a* is preferably configured such that the electrodes **38** have sufficient resilience to come into contact with the airway walls for treatment.

FIG. **5**B illustrates the treatment device **30***a* in which the distal end of the device is provided with a ball shaped member **50** for easily inserting the device to a treatment site without causing trauma to surrounding tissue. FIG. **5**C illustrates the treatment device **30***a* having electrodes **38** connected to the distal end of the catheter **36** and forming a basket shape. The basket shape may be expanded radially during use to insure contact between the electrodes **38** and the airway walls by pulling on a center pull wire **52** which is connected to a distal end **50** of the device and extends through a lumen of the catheter **36**. The treatment device **30***a* may be delivered to a treatment site through a delivery catheter or sheath **54** and may be drawn along the airway to treat the airway in a pattern of longitudinal or helical stripes.

FIG. **6** illustrates a treatment device **30***b* in which a catheter shaft **46** is provided with a plurality of electrodes **48**

positioned on inflatable balloons **50**. The balloons **50** are inflated through the catheter shaft **46** to cause the electrodes **48** come into contact with the airway walls **100**. The electrodes **48** are preferably connected to the energy source **32** by conductive wires (not shown) which extend from the electrodes through or along the balloons **50** and through the catheter shaft **46** to the energy source. The electrodes may be used in a bipolar mode without an external electrode. Alternatively, the treatment device **30***b* may be operated in a monopolar mode with an external electrode **44**. The electrodes **48** may be continuous circular electrodes or may be spaced around the balloons **50**.

An alternative treatment device **30***c* of FIG. **7** includes a catheter **56** having one or more grooves **60** in an exterior surface. Positioned within the grooves **60** are electrodes **58** for delivery of energy to the airway walls. Although the grooves **60** have been illustrated in a longitudinal pattern, the grooves may be easily configured in any desired pattern. Preferably, the treatment device **30***c* of FIG. **7** includes a biasing member (not shown) for biasing the catheter **56** against the airway wall such that the electrodes **58** contact the tissue. The biasing member may be a spring element, an inflatable balloon element, or other biasing member. Alternatively, the biasing function may be performed by providing a preformed curve in the catheter **56** which causes the catheter to curve into contact with the airway wall when extended from a delivery catheter.

FIG. **8** illustrates a treatment device **30***d* having one or more electrodes **68** connected to a distal end of a catheter **66**. The electrodes **68** are supported between the distal end of the catheter **66** and a device tip **70**. A connecting shaft **72** supports the tip **70**. Also connected between the distal end of the catheter **66** and the tip **70** is a spring element **74** for biasing the electrodes **68** against a wall of the airway. The spring element **74** may have one end which slides in a track or groove in the catheter **66** such that the spring can flex to a variety of different positions depending on an internal diameter of the airway to be treated.

FIG. **9** illustrates an alternative treatment device **30***e* in which the one or more electrodes **78** are positioned on a body **80** secured to an end of a catheter **76**. In the FIG. **9** embodiment, the body **80** is illustrated as egg shaped, however, other body shapes may also be used. The electrodes **78** extend through holes **82** in the body **80** and along the body surface. A biasing member such as the spring element **84** is preferably provided on the body **80** for biasing the body with the electrodes against the airway walls. Leads **85** are connected to the electrodes and extend through the catheter **76** to the energy source **32**.

FIGS. **10** and **11** illustrate a further treatment device **30***f* having one or more loop shaped electrodes **88** connected to a catheter shaft **86**. In the unexpanded position shown in FIG. **10**, the loop of the electrode **88** lies along the sides of a central core **90**. A distal end of the loop electrode **88** is secured to the core **90** and to an optional tip member **92**. The core **90** is slidable in a lumen of the catheter **86**. Once the treatment device **30***f* has been positioned with the distal end in the airway to be treated, the electrode is expanded by pulling the core **90** proximally with respect to the catheter **86**, as shown in FIG. **11**. Alternatively, the electrode **88** or the core **90** may be spring biased to return to the configuration of FIG. **11** when a constraining force is removed. This constraining force may be applied by a delivery catheter or bronchoscope through which the treatment device **30***f* is inserted or by a releasable catch.

The treatment device **30***g* of FIG. **12** includes a plurality electrodes **98** positioned on leaf springs **96** which are outwardly biased. The leaf springs **96** are connected to a shaft **102** which is positioned within a delivery catheter **94**. The leaf springs **96** and electrodes **98** are delivered through the delivery catheter **94** to a treatment site within the airways. When the leaf springs **96** exit the distal end of the delivery catheter **94**, the leaf springs bend outward until the electrodes **98** come into contact with the airway walls for application of energy to the airway walls.

FIGS. **13** and **14** illustrate embodiments of treatment devices **30***h*, **30***i* in which electrodes **106** in the form of wires are positioned in one or more lumens **108** of a catheter **104**. Openings **110** are formed in the side walls of the catheters **104** to expose the electrodes **106**. As shown in FIG. **13**, the treatment device **30***h* has multiple lumens **108** with electrodes provided in each of the lumens. The side wall of the treatment device **30***h* is cut away to expose one or more of the electrodes **106** through a side wall opening **110**. In FIG. **13**, the opening **110** exposes two electrodes positioned in adjacent lumens. The treatment device **30***h* may be provided with a biasing member as discussed above to bring the electrodes **106** of the device into contact with the airway wall.

The treatment device **30***i* of FIG. **14** includes a catheter **104** which has been formed into a loop shape to allow the electrode **106** to be exposed on opposite sides of the device which contact opposite sides of the airway. The resilience of the loop shape causes the electrodes to come into contact with the airway walls.

The treatment device **30***j* of FIG. **15** is in the form of a balloon catheter. The treatment device **30***j* includes electrodes **118** positioned on an exterior surface of an inflatable balloon **116**. The electrodes **118** are electrically connected to the energy source **32** by the leads **120** extending through the balloon and through the lumen of the balloon catheter **114**. The balloon **116** is filled with a fluid such as saline or air to bring the electrodes into contact with the airway wall **100**.

FIG. **16** shows an alternative embodiment of a balloon catheter treatment device **30***k* in which a fluid within the balloon **126** is heated by internal electrodes **128**. The electrodes **128** are illustrated in the shape of coils surrounding the shaft of the catheter **124**, however other electrode shapes may also be used. The electrodes **128** may be used as resistance heaters by application of an electric current to the electrodes. Alternatively, radio frequency or microwave energy may be applied to the electrodes **128** to heat a fluid within the balloon **126**. The heat then passes from an exterior of the balloon **126** to the airway wall. The radio frequency or microwave energy may also be applied indirectly to the airway wall through the fluid and the balloon. In addition, hot fluid may be transmitted to the balloon **126** from an external heating device for conductive heating of the airway tissue.

FIG. **17** illustrates a treatment device **30***m* for delivering heated fluid to the airway walls to heat the airway tissue. The device **30***m* includes a heating element **132** provided within a fluid delivery catheter **134**. The fluid passes over the heating element **132** and out of openings **136** in the end of the catheter **134**. The openings **136** are arranged to direct the fluid at the airway walls **100**. The heating element **132** may be a coiled resistance heating element or any other heating element. The heating element **132** may be positioned anywhere along the body of the catheter **134** or may be an external heating device separate from the catheter.

The heating element **132** may also be replaced with a friction producing heating element which heats fluid passing through the fluid delivery catheter **134**. According to one

embodiment of a friction producing heating element, a friction element rotates and contacts a stationary element for purposed of heating the fluid.

FIG. **18** illustrates a treatment device **30***n* for delivery of light or other radiant energy to the walls of the airway. The light delivery device **30***n* includes an outer catheter or sheath **140** surrounding a light transmitting fiber **142**. A light directing member **144** is positioned at a distal end of the light delivery device for directing the light to the airway walls. The sheath **140** includes a plurality of windows **146** which allow the light which has been redirected by the light directing member **144** to pass substantially radially out of the sheath. The light delivery device **30***n* is connected by a conventional optical connection to a light source **32**.

The light used may be coherent or incoherent light in the range of infrared, visible, or ultraviolet. The light source **32** may be any known source, such as a UV laser source. The light source **32** may be an ultraviolet light source having a wavelength of about 180–308 nm, a visible light source, or an infrared light source preferably in the range of 800–2200 nm. The intensity of the light may vary depending on the application. The light intensity should be bright enough to penetrate any mucus present in the airway and penetrate the airway walls to a depth necessary to treat the selected tissue. The light intensity may vary depending on the wavelength used, the application, the thickness of the smooth muscle, and other factors. The light or other radiant energy may also be used to heat an absorptive material on the catheter or sheath which in turn conductively heats the airway wall.

U.S. application Ser. No. 09/095,323 filed Jun. 10, 1998, illustrates different exemplary embodiments of the distal tip of the light delivery device **34***n* for irradiating the airway walls.

FIG. **19** shows an alternative embodiment of a treatment device **30***p* including a cryoprobe tip **150** for transferring or removing energy in the from of heat from an airway wall **100**. The cryoprobe tip **150** is delivered to the treatment site by a cryoprobe shaft **152**. Transfer of energy from the tissue structures of the airway wall can be used in the same manner as the delivery of energy with any of the devices discussed above. The particular configuration of the cryoprobe treatment device **30***p* may vary as is known in the art.

The treatment of the tissue in the airway walls by transfer of energy according to the present invention provides improved long term relief from asthma symptoms for some asthma sufferers. However, over time, some amount of smooth muscle or mucus gland cells which were not affected by an initial treatment may regenerate and treatment may have to be repeated after a period of time such as one or more months or years.

The airways which are treated with the methods according to the present invention are preferably 1 mm in diameter or greater, more preferably 3 mm in diameter or greater. The methods are preferably used to treat airways of the second to eighth generation, more preferably airways of the second to sixth generation.

Although the present invention has been described in detail with respect to methods for the treatment of airways in the lungs, it should be understood that the present invention may also be used for treatment of other body conduits. For example, the treatment system may be used for reducing smooth muscle and spasms of the esophagus of patients with achalasia or esophageal spasm, in coronary arteries of patients with Printzmetal's angina variant, for ureteral spasm, for urethral spasm, and irritable bowel disorders.

The methods according to the present invention provide a more effective and/or permanent treatment for asthma than the currently used bronchodilating drugs, drugs for reducing mucus secretion, and drugs for decreasing inflammation.

While the invention has been described in detail with reference to the preferred embodiments thereof, it will be apparent to one skilled in the art that various changes and modifications can be made and equivalents employed, without departing from the present invention.

What is claimed is:

**1**. A method for treating conditions of the lungs by decreasing airway responsiveness comprising:

transferring energy to or from an airway wall in the lungs to alter the airway wall in such a manner that the responsiveness of the airway is reduced.

**2**. The method of claim **1**, wherein the energy transfer alters the structure of the airway wall.

**3**. The method of claim **1**, wherein the energy transfer alters the function of the airway wall.

**4**. The method of claim **1**, wherein the method is used to treat asthma by preventing contraction of the airway.

**5**. The method of claim **1**, wherein the energy transfer alters the airway in such a manner that the ability of the airway to narrow is impaired.

**6**. The method of claim **1**, wherein the energy is transferred to the airway by moving an energy transfer device along the airway.

**7**. The method of claim **1**, wherein the energy is transferred to a portion of the airway by an energy transfer device which creates one or more energy transfer patterns.

**8**. The method of claim **7**, wherein the energy transfer pattern is a pattern of one or more spots having a rectangular, elliptical, circular, or other shape.

**9**. The method of claim **7**, wherein the energy is transferred to the airway in a band pattern covering a full diameter of the airway.

**10**. The method of claim **7**, wherein the energy is transferred to the airway in a pattern of at least one stripe extending along the airway in a longitudinal or helical pattern.

**11**. The method of claim **1**, wherein the energy is transferred to the airway at the location of an opening of an airway, a bifurcation, or an opening of a side branch.

**12**. The method of claim **1**, wherein the energy is transferred to the airway at a segment of the airway between bifurcations, openings, or side branches.

**13**. The method of claim **1**, wherein the energy is transferred to the airway by activating an energy transfer device, deactivating the energy transfer device, moving the energy transfer device, and reactivating the energy transfer device.

**14**. The method of claim **1**, wherein the energy transfer alters smooth muscle of the airway wall in such a manner that the responsiveness of the airway is reduced.

**15**. The method of claim **14**, wherein the ability of the smooth muscle to contract is altered.

**16**. The method of claim **15**, wherein shortening of all or some of the smooth muscle is reduced or prevented.

**17**. The method of claim **14**, wherein the energy transfer alters a connection between the smooth muscle and the airway wall.

**18**. The method of claim **14**, wherein the energy transfer eliminates at least a portion of the smooth muscle.

**19**. The method of claim **14**, wherein the energy transfer prevents the smooth muscle from replicating.

**20**. The method of claim **1**, wherein the energy transfer alters mucus producing cells or glands in the airway wall in such a manner that the responsiveness of the airway is reduced.

21. The method of claim 20, wherein the energy transfer eliminates at least a portion of the mucus producing cells or glands.

22. The method of claim 20, wherein the energy transfer prevents the mucus producing cells or glands from replicating.

23. The method of claim 20, wherein the energy transfer alters the ability of the mucus producing cells or glands to produce or secrete mucus.

24. The method of claim 1, wherein the energy transfer alters production or release of inflammatory mediators in at least a part of the airway.

25. The method of claim 24, wherein the energy transfer prevents replication of structures producing or releasing inflammatory mediators.

26. The method of claim 24, wherein the energy transfer eliminates at least a portion of the structures which produce or release inflammatory mediators.

27. The method of claim 24, wherein the energy transfer alters the ability of structures in the airway to produce or release inflammatory mediators.

28. The method of claim 1, wherein the energy transfer increases resistance to airway caliber reduction in at least a part of the airway.

29. The method of claim 28, wherein the increased resistance is produced by thickening or fibrosing the airway wall.

30. The method of claim 28, wherein the increased resistance is produced by increasing parenchymal tethering.

31. The method of claim 28, wherein the increased resistance is produced by increasing connection support between the airway and support structures.

32. The method of claim 1, wherein the energy transfer alters at least a part of the epithelium in the airway wall.

33. The method of claim 32, wherein the energy transfer eliminates epithelium.

34. The method of claim 32, wherein the energy transfer stimulates healing of the epithelium.

35. The method of claim 32, wherein the energy transfer stimulates replacement of the epithelium.

36. The method of claim 1, wherein the energy transfer alters at least a part of a submucosal layer in the airway wall.

37. The method of claim 36, wherein the energy transfer reduces a thickness of the submucosal layer.

38. The method of claim 1, wherein the energy transfer alters mucosal folding.

39. The method of claim 38, wherein the structure of the airway wall is altered by increasing a number of mucosal folds or decreasing a size of mucosal folds.

40. The method of claim 1, wherein a photodynamic agent is delivered to the airway wall and the energy transfer stimulates the photodynamic agent.

41. The method of claim 1, wherein the airways treated are at least 1 mm in diameter.

42. The method of claim 41, wherein the airways treated are at least 3 mm in diameter.

43. The method of claim 1, wherein the airways treated are generations 2 through 8.

44. The method of claim 43, wherein the airways treated are generations 2 through 6.

45. The method of claim 1, wherein the airway treated are visualizable with a bronchoscope.

46. A method for treating conditions of the lungs by decreasing airway resistance to airflow comprising:

transferring energy to or from an airway wall in the lungs to alter the airway wall in such a manner that a resistance to airflow of the airway is decreased.

47. The method of claim 46, wherein the energy transfer alters a structure of the airway wall to increase an effective caliber of the airway.

48. The method of claim 47, wherein the structure of the airway wall is altered by decreasing a thickness of the airway wall.

49. The method of claim 46, wherein the energy transfer alters a function of the airway wall to increase an effective caliber of the airway.

50. The method of claim 49, wherein the function of the airway wall is altered by reducing mucus or mucus plugging.

51. The method of claim 49, wherein the function of the airway is altered by reducing tissue inflammation.

52. The method of claim 51, wherein inflammation is reduced by reducing edema or healing epithelium.

53. The method of claim 49, wherein the function of the airway wall is altered by altering a resting tone of the airway wall.

54. The method of claim 53, wherein the resting tone is altered by altering the smooth muscle or by denervation.

* * * * *

# Appendix D

UNITED STATES PATENT AND TRADEMARK OFFICE

# CERTIFICATE OF CORRECTION

PATENT NO. : 6,411,852 B1
DATED : June 25, 2002
INVENTOR(S) : Christopher J. Danek et al.



It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Title page,
Item [75], Inventors, please add -- **Michael D. Laufer**, Menlo Park, California --.

Signed and Sealed this

Thirteenth Day of May, 2003

JAMES E. ROGAN
*Director of the United States Patent and Trademark Office*

2000 9,20

# Appendix E

UNITED STATES PATENT AND TRADEMARK OFFICE

# CERTIFICATE OF CORRECTION

64921.8011.US
PTP/MN





PATENT NO. : 6,411,852 B1
APPLICATION NO. : 09/296040
DATED : June 25, 2002
INVENTOR(S) : Christopher J. Danek et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Title page, Item (63), please replace:
"Continuation-in-part of application No. 09/095,323, filed on Jun. 10, 1998." with:
-- Continuation-in-part of application No. 09/095,323, filed on Jun. 10, 1998, continuation-in-part of application No. 08/994,064, filed on Dec. 19, 1997, now Pat. No. 6,083,255, continuation-in-part of application No. 09/224,937, filed on December 31, 1998, now Pat. No. 6,200,333, and a continuation-in-part of application No. 09/260,401, filed on Mar. 1, 1999, now Pat No. 6,283,988, which is a continuation-in-part of application No. 09/003,750, filed on Jan. 7, 1998, now Pat. No, 5,972,026, which is a continuation-in-part of application No. 08/833,550, filed on Apr. 7, 1997, now Pat. No. 6,273,907.--; and

In column 1, lines 4-6, please replace:
"This is a Continuation-in-part application of U.S. application Ser. No. 09/095,323 filed Jun. 10, 1998, which is incorporated herein by reference in its entirety." with:
-- This is a Continuation-in-part application of U.S. application Ser. No. 09/095,323 filed Jun. 10, 1998, which is incorporated herein by reference in its entirety, and is a Continuation-in-part application of U.S. application Ser. No. 08/994,064 filed Dec. 19, 1997, now U.S. Pat. No. 6,083,255, and is a Continuation-in-part application of U.S. application Ser. No. 09/224,937 filed December 31, 1998, now U.S. Pat. No. 6,200,333, and is a Continuation-in-part application of U.S. application Ser. No. 09/260,401 filed Mar. 1, 1999, now U.S. Pat. No. 6,283,988, which is a Continuation-in-part application of U.S. application Ser. No. 09/003,750 filed Jan. 7, 1998, now U.S. Pat. No. 5,972,026, which is a Continuation-in-part application of U.S. application Ser. No.08/833,550 filed Apr. 7, 1997, now U.S. Pat. No. 6,273,907.--

Signed and Sealed this

Thirteenth Day of November, 2007

JON W. DUDAS
*Director of the United States Patent and Trademark Office*

# Appendix F

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# MAINTENANCE FEE STATEMENT

The data shown below is from the records of the U.S. Patent and Trademark Office. If the maintenance fee and any necessary surcharge have been timely paid for the patent listed below, the notation "PAID" will appear in the "STAT" column.

If the statement of small entity status is defective the reason will be indicated below in the "Small Entity" status column. THE STATEMENT OF SMALL ENTITY STATUS WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION.

| PATENT NUMBER | FEE AMT | SUR CHARGE | U.S. APPLICATION NUMBER | PATENT ISSUE DATE | APPL. FILING DATE | PAYMENT YEAR | SMALL ENTITY? | STAT | ATTY DKT NUMBER |
|---|---|---|---|---|---|---|---|---|---|
| **6,411,852** | **$450.00** | **$0.00** | **09/296,040** | **06/25/02** | **04/21/99** | **04** | **YES** | **PAID** | **031201-025** |

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The payment shown below is subject to actual collection. If the payment is refused or charged back by a financial institution, the payment will be void and the maintenance fee and any necessary surcharge unpaid.

Direct any questions about this statement to: Mail Stop M Correspondence, Director of the USPTO, P.O. Box 1450, Alexandria, VA 22313-1450.

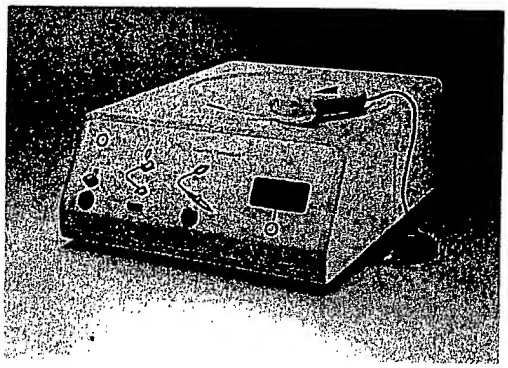
| PATENT NUMBER | FEE AMT | SUR CHARGE | PYMT DATE | U.S. APPLICATION NUMBER | PATENT ISSUE DATE | APPL. FILING DATE | PAYMENT YEAR | SMALL ENTITY? | ATTY DKT NUMBER |
|---|---|---|---|---|---|---|---|---|---|
| 6,411,852 | 1240 | 0 | 11/25/09 | 09/296,040 | 06/25/02 | 04/21/99 | 08 | YES | 649218011US |

# Appendix G

# ALAIR® | FOR BRONCHIAL THERMOPLASTY

## OPERATOR'S MANUAL

### Radiofrequency Controller
### Model ATS 200



℞ Only **United States federal law restricts this device to sale by or on the order of a physician.**

**The operator of the Alair® System must be a physician who has training and experience in performing bronchoscopic procedures.**

**This Operator's Manual is specific to the Alair® Controller Model ATS 200. Do not attempt to operate the Alair® Radiofrequency Controller before thoroughly reading this Operator's Manual and the Instructions for Use for the Alair® Catheter Model ATS 2-5.**

# Table of Contents

## ALAIR® BRONCHIAL THERMOPLASTY SYSTEM DESCRIPTION

This Operator's Manual provides instructions for using the Alair® Radiofrequency (RF) Controller Model ATS 200. The Alair® RF Controller Model ATS 200 is intended to be used with the Alair® Catheter. The Alair® RF Controller is designed to provide controlled delivery of radiofrequency energy to the Alair® Catheter. The Alair® RF Controller and the Alair® Catheter together comprise the Alair® Bronchial Thermoplasty System.

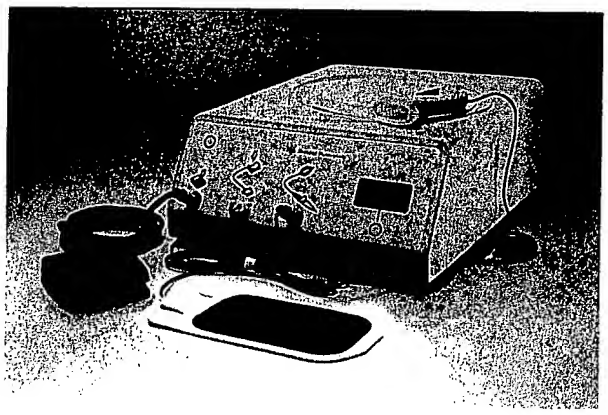


**Figure 1: The Alair® Bronchial Thermoplasty System**

The Alair® Bronchial Thermoplasty System ("Alair® System"), manufactured by Asthmatx, Inc. ("Asthmatx"), consists of the Alair® Controller System and the Alair® Catheter, as described below:

### Alair® Controller System

**Alair® Radiofrequency (RF) Controller:** The Alair® RF Controller Model ATS 200 ("Controller") is designed to provide controlled delivery of RF energy to the Alair® Catheter. Energy from the Controller is delivered to the Catheter through the electrical cable attached to the proximal end of the catheter handle. Actual power delivered is automatically modulated by the Controller based on temperature control algorithms. The Controller delivers low-power, temperature-controlled RF energy to the airway at a predetermined temperature setting for a predetermined time period. The Controller incorporates hardware and software features that limit current, voltage, power, energy, time and temperature during each application of RF energy. The Controller is not intended to come in contact with the patient and therefore is not provided as a sterile device.

**Footswitch:** The Controller is supplied with a footswitch that allows the operator to start and stop the delivery of RF energy. The Controller is designed to be used with the compatible footswitch provided by Asthmatx. The footswitch is not intended to come into contact with the patient and therefore is not provided as a sterile device.

**Patient Return Electrode:** The Controller is designed to be used with a gel-type patient return electrode that is compliant with the applicable portions of IEC 60601-2-2:2006 and/or CE marked. The patient return electrode is used to complete the return path for the electrical current. Use only patient return electrodes indicated for use with adults or patients weighing more than 15 kg (33 lbs). Examples of acceptable patient return electrodes include Valleylab E7506 and ConMed 51-7310. Follow the instructions for use (IFU) packaged with the patient return electrode.

## Alair® Catheter

The Alair® Catheter Model ATS 2-5 ("Catheter") is provided sterile and is a SINGLE-USE ONLY, disposable device. The Catheter delivers energy from the Controller to the desired site in the airway and relays temperature feedback to the Controller. The Alair® Catheter Model ATS 2-5 is designed to be used with the Alair® RF Controller Model ATS 200. For information on the preparation, use and other technical specifications, please refer to the Alair® Catheter Instructions for Use (IFU) that is supplied with Model ATS 2-5.

## INDICATION FOR USE

The Alair® Bronchial Thermoplasty System is indicated for the treatment of severe persistent asthma in patients 18 years and older whose asthma is not well controlled with inhaled corticosteroids and long-acting beta agonists.

## MECHANISM OF ACTION

Airway smooth muscle (ASM) consists of muscle tissue within the airway walls in the lung. Contraction of the ASM is a main cause of airway constriction that leads to difficulty in breathing during asthma attacks. Severe asthma patients also experience an increase in ASM mass. This increase, together with inflammation of the airways, combines to thicken airway walls, which decreases the inside diameter of the airways when the ASM contracts. The resulting decrease in airway diameter causes increased resistance to airflow and further contributes to difficulty in breathing during asthma attacks.

The Alair® System is used to deliver thermal energy to the airway wall, to heat the tissue in a controlled manner in order to reduce ASM mass. Bronchial thermoplasty is intended to reduce, debulk, or partially eliminate smooth muscle tissue. In preclinical studies (Danek et al. 2004[1], Brown et al. 2005[2]), the reduction of ASM has been shown to decrease the ability of the airways to constrict/contract, reduce resistance to airflow and responsiveness of the airway, and increase the resting diameter of the airway.

## CONTRAINDICATIONS, WARNINGS, AND PRECAUTIONS

### CONTRAINDICATIONS ⚠

Patients with the following conditions should not be treated:

- Presence of a pacemaker, internal defibrillator, or other implantable electronic devices,
- Known sensitivity to medications required to perform bronchoscopy, including lidocaine, atropine, and benzodiazepines,
- Patients previously treated with the Alair® System should not be retreated in the same area(s). No clinical data are available studying the safety and/or effectiveness of repeat treatments.

Patients should not be treated while the following conditions are present:

- Active respiratory infection,
- Asthma exacerbation or changing dose of systemic corticosteroids for asthma (up or down) in the past 14 days,
- Known coagulopathy,
- As with other bronchoscopic procedures, patients should stop taking anticoagulants, antiplatelet agents, aspirin and NSAIDS before the procedure with physician guidance.

[1] Danek CJ, Lombard CM, Dungworth DL, Cox PG, Miller JD, Biggs MJ, Keast TM, Loomas BE, Wizeman WJ, Hogg JC, Leff AR. Reduction in airway hyperresponsiveness to methacholine by the application of RF energy in dogs. J Appl Physiol. 2004, 97(5):1946-53

[2] Brown RH, Wizeman W, Danek C, Mitzner W. Effect of bronchial thermoplasty on airway distensibility. Eur Respir J. 2005 Aug;26(2):277-82.

## WARNINGS ⚠

**READ THIS OPERATOR'S MANUAL IN CONJUNCTION WITH THE ALAIR® CATHETER MODEL ATS 2-5 INSTRUCTIONS FOR USE BEFORE USING THE ALAIR® BRONCHIAL THERMOPLASTY SYSTEM. FAILURE TO FOLLOW ANY INSTRUCTIONS OR FAILURE TO HEED ANY WARNINGS OR PRECAUTIONS MAY RESULT IN HARM OR INJURY TO PATIENT.**

### Controller/RF Energy Warnings:

1. Do not use RF energy in the presence of flammable anesthesia or other flammable gases, flammable liquids (such as skin prepping agents and tinctures), or flammable objects. Non-flammable agents should be used for cleaning and disinfecting whenever possible. Flammable agents used for cleaning, disinfecting, or as solvents of adhesives, should be allowed to evaporate before the application of RF energy.
2. Do not use in oxygen-enriched atmospheres, nitrous oxide ($N_2 0$) atmospheres, or in the presence of other oxidizing agents.
3. Do not cut a patient return electrode to make it smaller as reducing the size of the patient return electrode may result in patient burns due to high current density.
4. Do not wrap the power cord, patient return electrode cord, or catheter cable around metal objects as hazardous currents may be induced leading to harm or injury (e.g. shock) to the patient or medical personnel, or fire.
5. While using this device, the patient should not be allowed to come into contact with grounded metal objects as harm or injury to the patient may result. Antistatic sheeting is recommended to prevent the patient from coming into contact with metal parts which are connected to earth or which have an appreciable capacitance to earth.
6. Skin-to-skin contact (e.g. contact between the arms and body of the patient) should be avoided by inserting dry gauze.
7. The electrical cord supplied for the Controller must be connected to a properly grounded receptacle. Do not use extension cords or adapters.
8. Exposing the Controller to liquids may result in harm or injury (e.g. electrical shock) to the patient and/or user or damage to the Controller.
9. Failure of the Controller may result in an unintended increase of output power.
10. When the Controller and physiological monitoring equipment are used simultaneously on the patient, any monitoring electrodes should be placed as far as possible from the patient return electrode. Needle monitoring electrodes are not recommended. In all cases, monitoring systems incorporating high frequency current-limiting devices are recommended.
11. The Controller should not be used adjacent to or stacked with other equipment. If adjacent or stacked use is necessary, the Controller should be observed to verify normal operation in the configuration in which it will be used. When RF energy is delivered, conducted and radiated electrical fields may interfere with other electrical medical equipment stacked with or placed adjacent to the Controller.
12. Do not open the Controller enclosure or tamper with the Controller in any way. Harm or injury (e.g. electrical shock) or damage to the Controller may result. Contact Asthmatx for repair/replacement.
13. Use of the Controller with a Non-Alair® Catheter may result in harm or injury to the patient and/or operator, or may result in product malfunction.

## Catheter Warnings:

1. Prior to performing the procedure, ensure appropriate training, equipment, medications and staff are in place to handle any potential bronchoscopic, respiratory or anesthesia related emergencies. The Alair® System should only be used in a fully equipped bronchoscopy suite with access to full resuscitation equipment to handle hemoptysis, pneumothorax, and other respiratory complications including acute exacerbation of asthma and respiratory failure requiring intubation.

2. Do not deliver energy if the Catheter's electrode array is in contact with a metal object. This may result in harm or injury to the patient and/or operator.

3. Do not advance the Catheter within the bronchoscope if significant resistance is felt, as this may result in harm or injury to the patient and/or cause damage to the Catheter and/or bronchoscope.

4. Do not advance the Catheter into bronchi in which the Catheter cannot be seen under bronchoscopic vision. Advancing the Catheter beyond this region may cause patient harm or injury such as pneumothorax or pneumomediastinum.

5. Do not reposition the bronchoscope with the Catheter advanced beyond the distal end of the bronchoscope as this may result in patient harm or injury.

6. Use of the Alair® Catheter with a non-Alair® Controller may result in harm or injury to the patient and/or operator, or may result in product malfunction.

7. Do not treat the right middle lobe because of the potential susceptibility of the right middle lobe to transient obstruction as a result of inflammation or edema due to certain anatomical characteristics. The narrow diameter of the lobar bronchus and acute take-off angle may create poor conditions of drainage that may cause patient harm or injury such as atelectasis or difficulty in re-inflation (Right Middle Lobe Syndrome).

## PRECAUTIONS ⚠

### Controller/RF Energy Precautions:

1. Alair® System components and accessories need to be rated for at least the maximum peak output voltage as specified in the Technical Specifications section of this manual. The Catheter designed for use with this Controller is rated for the maximum peak output voltage as specified in the Technical Specifications section of this manual.
2. Use a Valleylab E7506, ConMed 51-7310, or a similar gel-type patient return electrode that is compliant with the applicable portions of IEC 60601-2-2:2006 and/or CE marked. Use only patient return electrodes indicated for use with adults or patients weighing more than 15 kg (33 lbs).
3. Verify that all oxygen circuit connections are leak-free before and during the use of RF energy. Verify that the endotracheal tube (if used) is leak-free, and that the cuff is properly sealed to prevent oxygen leaks.
4. The RF delivery tones and indicator lights on the front panel are important safety features. Do not obstruct your view of the Controller's front panel.
5. Proper placement of a patient return electrode is required for the use of this device. Place the patient return electrode securely on the patient in accordance with manufacturer's instructions. Check the patient return electrode before and periodically during system use to ensure that it is in firm contact with the skin, especially whenever the patient is repositioned.
6. The Catheter cable should be positioned in such a way that contact with the patient return electrode cable or other wires is avoided.
7. The Alair® System needs special precautions regarding Electromagnetic Compatibility ("EMC"). Portable and mobile communications devices can affect proper operation of the Alair® System. The Alair® System should be installed and used in accordance with the EMC information provided in this Operator's Manual.
8. The use of components or accessories other than an Alair® Catheter, or as suggested by Asthmatx, may result in increased electromagnetic emissions or decreased electromagnetic immunity of the Controller.

## Catheter Precautions:

1. The Alair® Catheter is provided sterile and is SINGLE USE ONLY. Do not use the Catheter if the package is opened, torn, or damaged. Use of a Catheter from damaged packaging may result in patient harm or injury. **Do not re-sterilize or reuse** the Catheter, as this may result in patient harm or injury, transmittal of infectious disease or product malfunction.
2. Do not use the Catheter if it comes in contact with a surface that is not aseptic (e.g. floor). This may result in patient infection.
3. Do not use the Catheter if it is damaged or irregular. Use of a damaged or irregular Catheter may result in patient harm or injury.
4. Do not use the Catheter if the marker bands are missing.
5. Use care when handling the Catheter to avoid kinking the Catheter shaft.
6. Avoid deflecting the bronchoscope while the electrode array is within the bend of the bronchoscope's working channel as this may result in damage to the Catheter and failure of the Catheter to operate properly.
7. Before inserting or removing the Catheter from the bronchoscope, ensure the electrode array is relaxed. Do not use the Catheter if the electrode array does not expand or relax properly.
8. Before delivering energy, make certain that all electrodes are in contact with the airway wall.
9. Caution should be taken in patients with the following conditions due to a potential increased risk of adverse events that may be associated with the procedure. Patients with these conditions were not studied in the pivotal trial and the safety of Alair® treatment for such patients has not been determined:
    - Post-bronchodilator $FEV_1$ < 65% predicted.
    - Other respiratory diseases including emphysema, vocal cord dysfunction, mechanical upper airway obstruction, cystic fibrosis or uncontrolled obstructive sleep apnea.
    - Use of short-acting bronchodilator in excess of 12 puffs per day within 48 hours of bronchoscopy (excluding prophylactic use for exercise).
    - Use of oral corticosteroids in excess of 10 milligrams per day for asthma.
    - Increased risk for adverse events associated with bronchoscopy or anesthesia, such as pregnancy, insulin dependent diabetes, epilepsy or other significant co-morbidities, such as uncontrolled coronary artery disease, acute or chronic renal failure, and uncontrolled hypertension.
    - Intubation for asthma, or ICU admission for asthma within the prior 24 months.
    - Any of the following within the past 12 months:
        i. 4 or more lower respiratory tract infections (LRTI)
        ii. 3 or more hospitalizations for respiratory symptoms
        iii. 4 or more OCS pulses for asthma exacerbation
10. The Alair® System should only be used by clinicians who are experienced in bronchoscopy and have undergone adequate training with the device.
11. The Alair® System should only be used in patients stable enough to undergo bronchoscopy in the judgment of their clinician.
12. Follow local governing ordinances and your institution's biohazard procedures regarding disposal of the Alair® Catheter and patient return electrode.

## CLINICAL DATA

### *Objectives*

The pivotal study was a multi-center, randomized, double-blind, sham-controlled study to demonstrate the safety and effectiveness of the Alair® System in a population of subjects with severe asthma.

### *Effectiveness Endpoints*

The primary effectiveness endpoint was the difference between treatment (Alair) and control (Sham) groups in the change in the Asthma Quality of Life Questionnaire (AQLQ) score between baseline and the average of 6-, 9-, and 12-month follow-up visits (integrated AQLQ score). Other endpoints included: rates of severe asthma exacerbations, proportions of patients with severe asthma exacerbations, and days lost from work, school, or other daily activities due to asthma symptoms. In addition, several safety endpoints were considered for effectiveness; these endpoints included rates of asthma (multiple symptoms)* adverse events, Unscheduled Physician Office visits for respiratory symptoms, Emergency Room visits for respiratory symptoms, and Hospitalizations for respiratory symptoms.

* "Asthma (multiple symptoms)" is defined as occurrence or worsening of shortness of breath, wheeze, cough, productive cough, or some combination of these.

### *Methods*

This was a multicenter, randomized (2 Alair, 1 Sham), double-blind, sham-controlled clinical trial comparing the effects of treatment with the Alair® System to a Sham treatment in subjects that were optimized to conventional therapy of inhaled corticosteroids (ICS) and long-acting $\beta_2$-agonists (LABA). All subjects included in the Study were taking ICS (> 1000µg beclomethasone or equivalent per day) and LABA (≥ 100µg salmeterol or equivalent per day), and were still symptomatic.

Subjects in the Alair and Sham groups were administered the Alair® treatment and Sham bronchoscopies, respectively, by an unblinded bronchoscopy team in 3 separate bronchoscopy sessions. Each bronchoscopy session was separated by at least 3 weeks. All bronchoscopy sessions were administered under local anesthesia with sedation. Subjects had follow-up visits with blinded asthma assessment teams at 6-weeks, 12-weeks, 6-months, 9-months, and 12-months after the final bronchoscopy session.

All subjects were prescribed to take 50mg of oral prednisone or prednisolone (or equivalent) each day for 5 days covering the 3 days before the bronchoscopy session, the day of the bronchoscopy session, and the day after the bronchoscopy session (prophylactic indication).

### *Statistical Plan*

Primary and secondary endpoints, as well as adverse events were analyzed using Bayesian statistics. The Posterior Probability of Superiority was calculated for the primary and secondary endpoints, as well as safety outcomes.

### *Patient Population*

Enrollment was limited to patients with severe persistent asthma who were still symptomatic despite being managed on conventional therapy of high dose ICS and LABA. Subjects may have been taking up to 10 milligrams of oral corticosteroids per day. Study subjects were required to meet the following patient selection criteria:

### Key Entry Criteria

### Inclusion

1. Adult; age 18-65 years.
2. Asthma requiring regular maintenance medication that includes inhaled corticosteroids (greater than 1000µg beclomethasone per day or equivalent) and long-acting β2-agonists (at least 100µg salmeterol per day or equivalent), with or without other asthma medications. Oral corticosteroids at a dosage of up to, but not greater than 10mg per day, or 20 milligrams every other day are acceptable.
3. Asthma Quality of Life Questionnaire Score during the Baseline Phase of 6.25 or less.

4. Pre-bronchodilator forced expiratory volume in one second ≥60% predicted (after patients stabilized on inhaled corticosteroids and long-acting β2-agonists during the Baseline Phase).
5. Non-smoker x 1 year or greater (if former smoker, less than 10 pack years total smoking history).

**Exclusion**

1. Post-bronchodilator $FEV_1$ <65% predicted.
2. Three or more hospitalizations for exacerbations of asthma in the previous year; OR a history of life-threatening asthma, defined by past intubations for asthma, or intensive care unit admission for asthma within the prior 24 months.
3. History of recurrent lower respiratory tract infection requiring antibiotics (more than 3 in the past 12-Months).
4. History of recurrent oral steroid use for asthma (4 or more pulses of oral steroids in the past 12-Months).

### *Demographics*

A total of 297 subjects between the ages of 18 and 65 were enrolled and randomized (2 Alair: 1 Sham) in this study. One hundred and ninety (190) subjects received the Alair® treatment and 98 subjects received the Sham control treatment (Intent-to-Treat population). The Sham procedure was identical to the Alair® procedure except that no energy was delivered through the Catheter.

There were no statistical differences in demographic measures between the Alair and Sham groups. Subject demographics are described in **Table 1**.

| | Alair (n=190) | Sham (n=98) |
|---|---|---|
| Age (years) (Mean ± SD) | 41 ± 12 | 41 ± 12 |
| Gender | | |
| Male | 81 (43%) | 38 (39%) |
| Female | 109 (57%) | 60 (61%) |
| Race/Ethnicity | | |
| Caucasian | 151 (80%) | 72 (74%) |
| African American / Black | 19 (10%) | 15 (15%) |
| Hispanic | 6 (3%) | 4 (4%) |
| Asian | 4 (2%) | 1 (1%) |
| Other | 10 (5%) | 6 (6%) |
| Height (cm) (Mean ± SD) | 167 ± 9 | 167 ± 10 |
| Weight (kg) (Mean ± SD) | 82 ± 18 | 82 ± 20 |

**Table 1: Subject Demographics (Intent-to-Treat Population)**

### *Effectiveness Results*

Effectiveness analyses were performed for both the Intent-to-Treat (ITT) population and Per-Protocol (PP) population. The ITT population consisted of all randomized subjects who have been administered at least one bronchoscopy. The PP population excluded all subjects in the ITT population who met any of the following criteria:

- Have taken any interfering concomitant medications.
- Have undergone other interfering treatments.
- Did not attend one of the 6-, 9-, 12-month visits, with the exception of a discontinuation from the Study due to an adverse event related to Study treatment.
- Had missed one or more bronchoscopy procedures.

***Effectiveness Endpoints***

Although the clinical study was powered only for the primary effectiveness endpoint (see below), several effectiveness endpoints and safety endpoints that could also be considered effectiveness endpoints demonstrated clinically meaningful differences in favor of the Alair group compared to the Sham group. The effectiveness endpoints were rates of severe asthma exacerbations, proportions of patients with severe asthma exacerbations, and days lost from work, school, or other daily activities due to asthma symptoms. The safety endpoints considered for effectiveness were rates of asthma, emergency room visits for respiratory symptoms, and hospitalization rates for respiratory symptoms.

**Steroid Exacerbations[a] (Severe Exacerbations Requiring Systemic Corticosteroids) (ITT Population):** During the Post-Treatment Phase, the severe exacerbation rate for the Steroid Exacerbations was 0.48 exacerbations/subject/year in the Alair group and 0.70 exacerbations/subject/year in the Sham group [95% CI (Sham - Alair): -0.031, 0.520]. During the Post-Treatment Phase, the proportion of subjects experiencing Steroid Exacerbations was 26% in the Alair group and 40% in the Sham group [95% CI (Sham - Alair): 2.1%, 25.1%].

Steroid Exacerbation rates (annualized rate) and proportion of patients experiencing Severe Exacerbations for the Post-Treatment Phase are presented graphically in **Figure 2**.

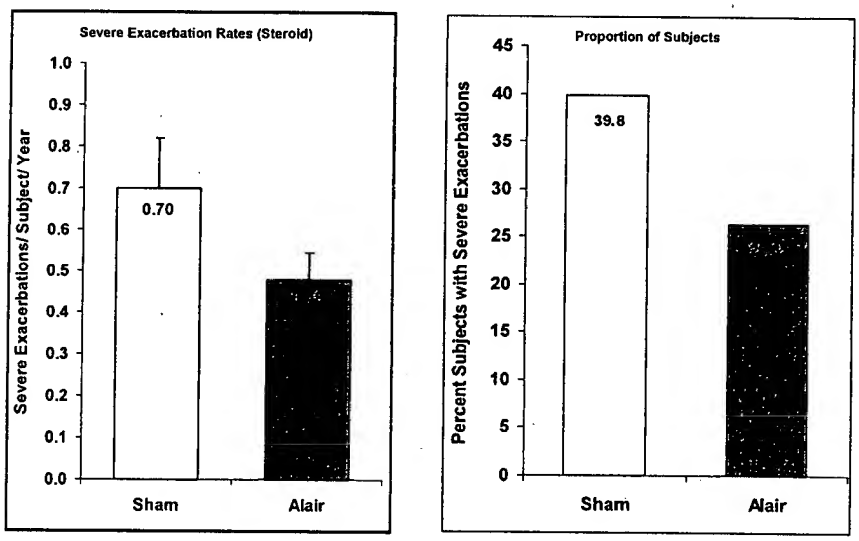



**Figure 2: Severe Exacerbations during the Post-Treatment Phase**

[a] **Steroid Exacerbations** = Exacerbations treated with oral or intravenous corticosteroids, OR a doubling of the baseline inhaled corticosteroid dose for at least 3 days, OR any temporary increase in the dosage of oral corticosteroids for a subject taking maintenance oral corticosteroids at Study entry.

Annualized rates of exacerbations per subject are extrapolated from the 46 week Post-Treatment Phase from 6 weeks after the last bronchoscopy procedure to the 12 month follow-up visit.

**Days Lost from Work, School, or Other Daily Activities due to Asthma Symptoms (ITT Population)**

During the Post-Treatment Phase, subjects in the Alair group lost an average of 1.3 days/year/subject from work, school, or other daily activities due to asthma symptoms, compared to the Sham group that lost 3.9 days/year/subject (annualized rates per subject are extrapolated from the 46 week Post-Treatment Phase from 6 weeks after the last bronchoscopy procedure to the 12 month follow-up visit) [95% CI (Sham - Alair): 0.425, 6.397].

***Safety Endpoints that Demonstrated Effectiveness***

Measures such as Emergency Room visits and Hospitalizations for respiratory symptoms are generally considered to be important measures of safety, especially if an intervention results in an increase in the rate of one or more of these events. However, these measures can also be considered important measures of effectiveness if an intervention results in a measurable decrease in the rate of one or more of these events. During longer-term follow-up (> 6 weeks after the last Alair® treatment), there was a reduction in asthma (multiple symptoms) adverse events [95% CI (Sham - Alair): -0.01, 0.001], Emergency Room visits for respiratory symptoms [95% CI (Sham - Alair): 0.11, 0.83], and Hospitalizations for respiratory symptoms (event rate per group) [95% CI (Sham - Alair): 0.025, 0.172], presented graphically in **Figure 3**.

There was a reduction in the proportion of subjects having asthma (multiple symptoms) adverse events [95% CI (Sham - Alair): 4.0%, 27.3%], and in the proportion of subjects having Emergency Room visits for respiratory symptoms in the Alair group (3.7% in the Alair group compared to 15.3% in the Sham group) [95% CI (Sham - Alair): 4.6%, 19.7%].

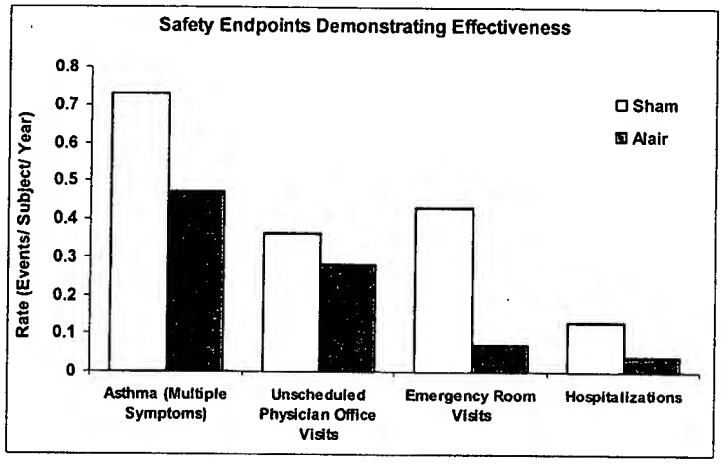



**Figure 3: Safety Endpoints demonstrating Effectiveness (ITT Population)**

***Primary Effectiveness Endpoint – Integrated AQLQ Score***

The difference between the Alair and Sham groups in the average change in AQLQ score from Baseline at the 6-, 9-, and 12-month follow-up visits was 0.210 [95% CI (Alair - Sham): -0.025, 0.445]. The pre-specified Posterior Probability of Superiority for the difference between the groups was 96.4%. For the ITT population, the difference between the groups had a Posterior Probability of Superiority of 96.0%, and for the PP population, the difference between the groups had a Posterior Probability of Superiority of 97.9%, demonstrating an improvement in the Asthma Quality of Life in the Alair group compared to Sham.
The results for the change from Baseline of the Integrated AQLQ score for the Intent-to-Treat and Per

Protocol populations are summarized in **Table 2**.

| Population | Difference Between Groups in Integrated AQLQ Score (Posterior Mean, 95% CI) | Posterior Probability of Superiority (%) |
|---|---|---|
| **ITT (Intent-to-Treat)** (Alair N=190, Sham N=98) | 0.210 (-0.025, 0.445) | 96.0 |
| **PP (Per Protocol)** (Alair N=173, Sham N=95) | 0.244 (0.009, 0.478) | 97.9 |

**Table 2: Primary Effectiveness Endpoint: Integrated AQLQ Score**

## ADVERSE EVENTS IN PIVOTAL STUDY

### Patient Population

The Alair® System was evaluated in a randomized, double-blind, sham-controlled, multi-center clinical study – the Asthma Intervention Research 2 (AIR2) Trial. A total of 297 subjects with severe persistent asthma who were still symptomatic despite being managed on conventional therapy of high dose ICS and LABA were randomized – 196 subjects in the Alair group and 101 subjects in the Sham group. (See the Clinical Data section for key entry criteria.) The Sham procedure was identical to the Alair® procedure except that no energy was delivered to the Catheter in the sham procedure.

Safety analyses were performed for the Intent-to-Treat (ITT) population (288 subjects) that consisted of all randomized subjects who have been administered at least one bronchoscopy.

### Observed Adverse Events

The safety of the Alair® System was assessed by comparing adverse event profiles of the Alair and Sham group subjects. Adverse event profiles are compared for the Treatment Phase (day of first bronchoscopy procedure to 6 weeks after the last bronchoscopy procedure) and Post-Treatment Phase (6 weeks after the last bronchoscopy to the 12 month follow-up visit).

Adverse events (whether considered procedure-related or not procedure-related by the investigator) occurring with ≥ 3% incidence that were more common in the Alair group are presented for 288 patients in **Table 3**.

| Adverse Event | Treatment[3] | | Post-treatment[4] | |
|---|---|---|---|---|
| | Alair (N=190) % | Sham (N=98) % | Alair (N=187) % | Sham (N=98) % |
| **Average duration of period (days)** | 84 | | 322 | |
| **Ear, Nose, and Throat** | | | | |
| Upper respiratory tract infection | 20 | 11 | 30 | 26 |
| Viral Upper respiratory tract infection | 4 | 2 | 6 | 7 |
| Nasopharyngitis | 5 | 7 | 11 | 5 |
| Acute Sinusitis | 3 | 2 | 4 | 8 |
| Rhinitis | 2 | 0 | 4 | 6 |
| **Lower Respiratory** | | | | |
| Asthma (Multiple Symptoms) | 52 | 39 | 27 | 43 |
| Wheezing | 15 | 6 | 4 | 3 |
| Dyspnea | 11 | 6 | 2 | 1 |
| Bronchitis | 4 | 2 | 7 | 5 |
| Chest discomfort | 9 | 10 | 2 | 1 |
| Atelectasis | 5 | 0 | 0 | 0 |
| Hemoptysis | 3 | 0 | 0 | 0 |
| Lower respiratory tract infection | 8 | 2 | 3 | 6 |
| Chest pain | 14 | 13 | 3 | 1 |
| **Neurology** | | | | |
| Anxiety | 4 | 0 | 1 | 2 |
| Headaches | 14 | 9 | 5 | 3 |
| **Gastrointestinal** | | | | |
| Dyspepsia | 4 | 2 | 2 | 4 |
| Nausea | 3 | 4 | 1 | 1 |
| **Non-site specific** | | | | |
| Pyrexia (fever) | 4 | 2 | 0 | 1 |
| Influenza | 4 | 2 | 4 | 12 |
| **Other** | | | | |
| Urinary tract infection | 1 | 1 | 3 | 1 |
| Hypertension | 3 | 2 | 3 | 3 |

**Table 3: Adverse Events with ≥ 3% Incidence (% of subjects) that were more common in the Alair Group**

**Adverse events occurring in both the Treatment Phase and Post-Treatment Phase at a rate of <3% and ≥1% (whether considered procedure-related or not procedure-related by the investigator) that were more frequently reported by the Alair group than the Sham group included pneumonia, operative hemorrhage, abnormal breath sounds, bronchial obstruction, acute bronchitis, bronchospasm, lower respiratory tract infection (viral), pulmonary congestion, discolored sputum (blood-tinged sputum), increased upper airway secretion, and viral pharyngitis.**

During the Treatment Phase in the AIR2 Trial, there was a transient increase in respiratory adverse events, including asthma (multiple symptoms), upper respiratory tract infection, atelectasis, lower respiratory tract infection, wheezing, hemoptysis, and anxiety in the Alair group compared to the Sham group. There was a lower incidence of throat irritation in the Alair group compared to the Sham group. There were 7 instances of hemoptysis defined as >5.0 mL (1.3% of bronchoscopies) of which 2 occurred on the day of the procedure, 2 occurred within 3 days, 2 occurred at 2 weeks, and one occurred on Day 31 after the procedure. The greatest amount of hemoptysis observed was a cumulative total of 150 mL that occurred over 5 days and was treated with bronchial artery embolization.

During the Treatment Phase (~ 12 weeks period), the rate of Unscheduled Physician Office visits (events / subject / 12 weeks) in the Alair group was 0.230 compared to 0.133 in the Sham group. The rate of hospitalizations for respiratory symptoms (events / subject / 12 weeks) was 0.086 in the Alair group compared to 0.028 in the Sham group. The rate of Emergency Room visits for respiratory symptoms (events / subject / 12 weeks) was 0.062 in the Alair group compared to 0.075 in the Sham group.

3 Treatment phase represents adverse events reported between the first bronchoscopy and 6-weeks post last bronchoscopy.
4 Post-Treatment phase represents adverse events reported between 6-weeks post last bronchoscopy and the 12 month visit.

During the Post-Treatment Phase in the AIR2 Trial, there was a lower incidence of respiratory symptoms in the Alair group compared to the Sham group, including a 36% reduction in asthma (multiple symptoms) events and proportion of subjects with asthma (multiple symptoms) events. There was also a lower incidence of influenza, and a greater incidence of nasopharyngitis in the Alair group compared to the Sham group.

**High Resolution Computed Tomography (HRCT) Results**
In the 150 subjects (100 Alair group and 50 Sham group) assigned to HRCT scan examinations, at 1-year, there were no difference in signs of gas trapping or consolidation and there was no evidence of bronchiectasis. A difference was seen in bronchial wall thickening without gas trapping which occurred only in the Sham subjects (4%).

**Summary of Clinical Findings**
Results from the clinical study which evaluated the effectiveness and safety of the Alair® System in subjects with severe asthma demonstrated that Alair® treatment resulted in clinically significant reductions in severe exacerbations that required systemic steroids, the percent of subjects experiencing the severe exacerbations, the number of Emergency Room visits for respiratory symptoms, the percent of subjects experiencing Emergency Room visits for respiratory symptoms, Hospitalizations for respiratory symptoms, and days lost from school/work/other daily activities due to asthma symptoms. Although bronchial thermoplasty was associated with an increased rate of respiratory adverse events during the Treatment Phase (primarily related to asthma), in the Post-Treatment Phase, a smaller proportion of patients treated with bronchial thermoplasty experienced respiratory adverse events, including asthma (multiple symptoms).

## INSTALLATION

Inspect the Controller for any signs of physical damage. If physical damage is found, do not use. Please contact Asthmatx for repair/replacement.

## PREPARING THE ALAIR® CONTROLLER FOR USE

The Controller should be placed on a sturdy cart, table, or platform. Provide at least four to six inches of space around the sides and top of the Controller to allow adequate ventilation. It is normal for the top and rear panel to be warm under continuous use.

## POWER CORD

The Controller is shipped with an approved hospital-grade power cord. Do not use extension cords or adapters.

## PROPER GROUNDING

To ensure patient safety, the Controller must be properly grounded. The ground wire in the power cord is connected to the Controller chassis and ensures that no dangerous currents will flow from the Controller chassis in the event of internal electrical failure.

## ROUTINE INSPECTIONS AND MAINTENANCE

The power cord assembly should be periodically checked for damage to the insulation or connectors. In the event that the Controller requires repair/replacement, please contact Asthmatx. If needed, only your institution's biomedical engineering representatives should replace the Controller fuses. Routine maintenance and calibration of the Controller are not required.

## CLEANING AND DISINFECTING INSTRUCTIONS

Disconnect the power cord before cleaning or disinfecting the unit. Use a mild non-abrasive detergent or cleaning/disinfecting solution and damp cloth to clean the Controller enclosure, front panel, and power cable. Do not allow fluids to enter the enclosure, power cable connections, or component/accessory connections. Do not attempt to clean the unit while it is plugged into an electrical outlet.

> ***Note:*** *Do not spray or pour liquid onto the Controller. Exposure of the Controller to liquids may result in electrical shock to the user or damage to the Controller.*

## FRONT PANEL INDICATORS, DISPLAY, AND RECEPTACLES

A description of the front panel indicators, control buttons and their functions is given below. Please refer to **Figure 4** for the location of each item on the front panel.

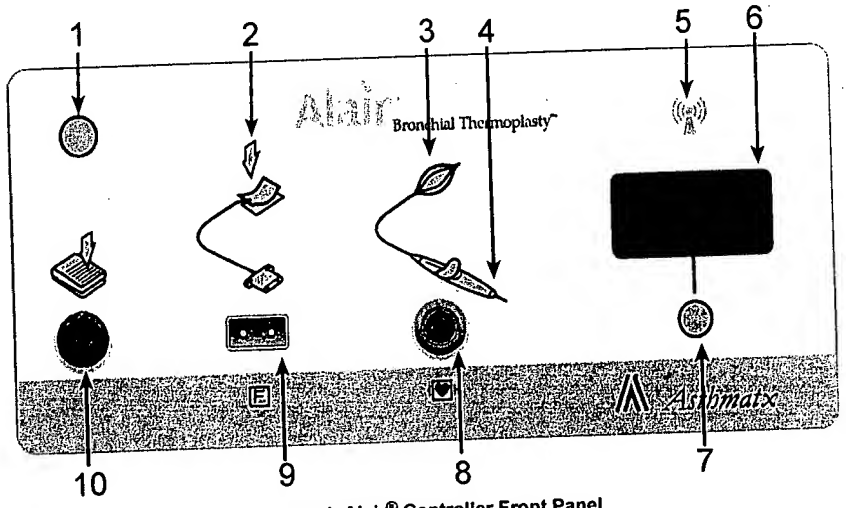



**Figure 4: Alair® Controller Front Panel**

## INDICATORS

1. **Status Indicator** – This indicator gives the user a signal about the overall readiness of the Alair® System. When the Status Indicator light is *green* the Controller is in READY mode and able to deliver RF energy.

   When the Status Indicator light is *amber* the Controller is in STANDBY mode and is not capable of delivering RF energy. More detail on the Controller modes is provided below.

2. **Patient Return Electrode Icon** – When the Patient Return Electrode Icon light is *amber* the user should ensure that the patient return electrode gel pad is correctly applied to the patient.

   After ensuring proper electrode placement, proceed by re-expanding the Catheter electrode array, taking care to ensure proper contact of all electrodes with the airway wall, and ensuring minimal movement of the electrode array during delivery of RF energy; then, continue.

3. **Catheter Electrode Array Icon** – When the Catheter Electrode Array Icon light is *amber* the user should re-expand the Catheter electrode array, taking care to ensure proper placement and contact of all electrodes with the airway wall and ensuring minimal movement of the electrode array during delivery of RF energy; then, continue.

4. **Catheter Handle Icon** – When the Catheter Handle Icon is flashing *red* the Catheter should be discarded and replaced with a new Catheter.

5. **RF Energy Icon** – When the RF Energy Icon light is *blue* the Controller is delivering RF energy. This icon lights only while RF energy is being delivered.

## DISPLAY

6. **Activation Counter Digital Display** – Displays the number of complete activations performed during device use.

7. **Activation Counter Button** – When the counter button is depressed and released, the counter displays the number of incomplete activations for 5 seconds.

   When the counter button is depressed and held for 4 seconds, the complete and incomplete activation counters are reset to zero.

   ***Note:*** *The activation counter will not reset during the display of incomplete activations. Reset the activation counter only during the display of complete activations.*

## RECEPTACLES

8. **Catheter Receptacle** – The *grey* receptacle accepts Catheter connectors and is keyed to ensure proper orientation. This connector is isolated from ground and AC mains to protect the patient from electrical hazards.

9. **Patient Return Electrode Receptacle** - This receptacle accepts any standard, 2-pin patient return electrode connector. This connector is isolated from ground and AC mains to protect the patient from electrical hazards.

10. **Footswitch Receptacle** – The *black* footswitch receptacle accepts the footswitch connector and is keyed to insure proper orientation. A single activation of the footswitch will turn the RF output ON if it was OFF, and turn the RF output OFF if it was ON.

## REAR PANEL INDICATORS AND FUNCTIONS

A description of the rear panel indicators and functions is given below. Please refer to **Figure 5** for the location of each item on the rear panel.

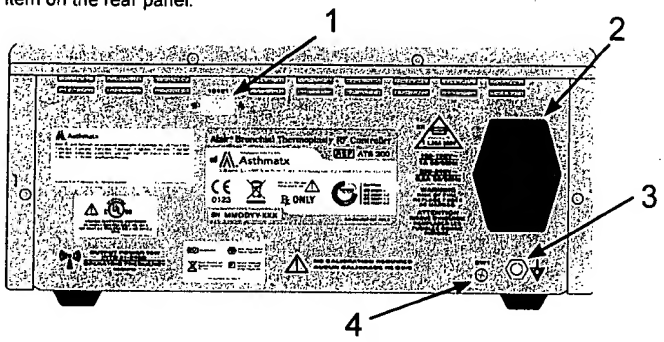



**Figure 5: Alair® Controller Rear Panel**

1. **Serial Communication Port** – For service by authorized personnel only. Not for use by user.
2. **Power Entry Module** – This module contains both the ON/OFF switch (I/O) and the power connection.
3. **Equipotentiality Connector** – Provides a means of securely linking the chassis of the Controller to the potential equalization system at the installation site.
4. **Program Memory Enable Screw** – For service by authorized personnel only. Not for use by user.

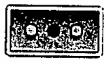
## INSTRUCTIONS FOR USE

### ALAIR® CONTROLLER POWER-UP

1. Plug the Controller into a grounded receptacle. Do not use extension cords or adapters.
2. Turn the power on using the ON/OFF switch that is located on the Power Entry Module on the rear panel of the Controller **(see Figure 5 above)**. The Controller will perform a number of internal self-tests: a tone will sound and all indicators will light for approximately 1 second. Do not use the Controller if any of the indicators fails to light or this tone is not heard. In the event of malfunction, contact Asthmatx for repair or replacement.
3. Once the self-test is completed, the Controller will enter STANDBY mode with the digital display showing zero [0] and the Status Indicator illuminated *amber* **(refer to Figure 4 above for the location of all controls and indicators)**.
4. The Status Indicator light will transition from *amber* to *green* once all component and accessory connections have been made.
5. If the Controller goes directly into FAULT mode with all lights flashing upon start-up (see the Controller Modes section below for explanation of FAULT mode conditions), turn the Controller power switch OFF and ON again. If the Controller continues to enter the FAULT mode contact Asthmatx for repair or replacement information.

## CONNECTION OF ALAIR® SYSTEM COMPONENTS AND ACCESSORIES

1. Connect a suitable, 2-pin patient return electrode to the corresponding electrode receptacle on the front panel of the Controller following the manufacturer's IFU **(see illustration at right)**. This receptacle has a patient return electrode icon directly above it. Place the patient return electrode securely on the patient in accordance with the patient return electrode manufacturer's instructions.



2. Connect the *black* footswitch cable connector supplied with the Controller to the matching *black* footswitch receptacle on the front panel of the Controller **(see illustration at right)**. The appropriate receptacle has a footswitch icon directly above it.

3. Connect the *grey* Catheter electrical cable to the matching *grey* catheter receptacle on the Controller front panel **(see illustration at right)**. The appropriate receptacle has a catheter icon directly above it.

4. If all the component and accessory connections have been made and the Controller has been powered ON, the Status Indicator light will be *green* **(see illustration at right)**. If the Catheter, or footswitch, or return electrode connections described above have <u>not</u> been completed, the Controller will remain in the STANDBY mode and the Status Indicator light will remain *amber*.

## ALAIR® CONTROLLER MODES

**SELF-TEST Mode** – This mode lasts approximately 2 seconds and occurs automatically upon turning on the power to the Controller. The Controller performs a number of internal tests to verify correct functioning of the Controller. All of the indicators should light and the digital display should show [188]. A long tone should be heard during the SELF-TEST. This mode automatically transitions to either STANDBY or READY mode when it is completed.

**STANDBY Mode** – The STANDBY mode indicates that the Controller has passed its SELF-TEST and is standing by for component and accessory connections to be made in preparation for use. The Status Indicator light is *amber* when the Controller is in STANDBY mode. This mode is entered automatically after the SELF-TEST mode if any of the components or accessories (Catheter, footswitch, or patient return electrode) are not connected to the Controller.

**READY Mode** – The READY mode indicates that all required component and accessory connections (Catheter, footswitch, and patient return electrode) have been made and that the Controller is ready to deliver energy. The Status Indicator light is *green* when the Controller is in READY mode.

**RF ON Mode** – RF energy is being delivered in this mode. The RF Energy Icon light is *blue* when RF energy is being delivered. When the footswitch is depressed a short tone signals the start of RF energy delivery, and an intermittent dual tone sounds at 2-second intervals during RF energy delivery. The Controller delivers energy until the activation is complete or until the footswitch is depressed a second time, discontinuing RF energy delivery. After the completion of each activation, a long tone signals the termination of RF energy delivery and the Controller returns to the READY mode.

**FAULT Mode** – This mode indicates that a safety algorithm has been triggered or a non-recoverable error has occurred. In the case of a non-recoverable error, the digital display will flash [188] and all other indicators will flash. A non-recoverable error can only be reset by turning the Controller off, then on again. If FAULT mode persists, please contact Asthmatx for repair or replacement information.

## PERIODIC MAINTENANCE AND REPAIR

Routine maintenance and calibration of the Controller are not required. The power cord assembly should be periodically checked for damage to the insulation or connectors. Also, check the Troubleshooting section below in case of Controller malfunction.

In the event that the Controller requires repair or replacement, please contact Asthmatx.

Only a qualified biomedical engineering representative at your institution should replace the Controller fuses.

## TROUBLESHOOTING

If you encounter problems while using the Controller, check the following:

| Problem/Error Message | Check the following |
|---|---|
| Controller does not power on | • Ensure that the switch at the rear of the Controller is in the "ON" position<br>• Check power cord connection at the rear of the Controller<br>• Check that the Controller power cord is connected to an appropriate power supply (see the Technical Specifications Section).<br>• Have a qualified biomedical engineering representative at your institution check the Controller fuses or contact Asthmatx for repair or replacement information. |
| The status indicator does not transition from the Standby Mode (*amber*) to the Ready Mode (*green*) | • Ensure that the Alair® Catheter, patient return electrode and footswitch are all properly connected to the Controller |
| RF Energy is not delivered when the footswitch pedal is depressed | • Check that the Controller is powered on<br>• Ensure that the Alair® Catheter, the patient return electrode and footswitch are all properly connected to the Controller |
| Catheter icon on Controller is flashing *red* and the Controller is not responding | • Replace the Alair® Catheter with a new Alair® Catheter |

If any of these problems persist, please contact Asthmatx for repair or replacement information.

## TECHNICAL SPECIFICATIONS

According to the IEC 60601-1 standard for medical devices, the Controller is classified as Class 1 equipment.

**RF OUTPUT (not user adjustable)**

Waveform - 461 kHz, sinusoidal

Maximum Output Values

- Power: 25 Watts; limited by software to 18 watts
- Voltage: 85 Vrms
- Current: 0.90 Arms

Maximum Power Output over the Range of Load Resistance (see **Figure 6**): Actual power delivered will be automatically adjusted by the Controller based on temperature control algorithms.

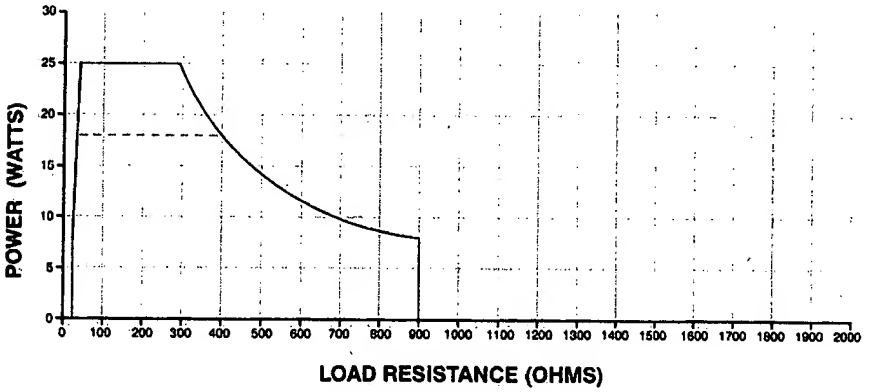



**Figure 6: Maximum Power Given Load Resistance**

## SHUTDOWN LIMITS

- Measured Temperature: < 10°C or > 15°C above set temperature
- Measured Impedance: < 25Ω, or > 900Ω

## MECHANICAL SPECIFICATIONS

- Size: 5.3 in x 12.3 in x 15.4 in (13.5 cm x 31.2 cm x 39.1 cm)
- Measured Temperature Accuracy: ± 0.5% ± 2.5°C
- Weight: 12.5 lbs. (5.6 kg)

## ENVIRONMENTAL STORAGE AND TRANSPORT CONDITIONS

- Storage temperature: 10°C to 40°C
- Transportation conditions: -40°C to 70°C
- Ensure that the unit is at room temperature for one hour before use if unit has been exposed to extreme temperature conditions

## AC INPUT SPECIFICATIONS

- 100 – 120 V~ 50/60 Hz, 1.0 A
- 220 – 240 V~ 50 Hz, 0.5 A

Replace mains fuses as marked: 1.25A/250V, T-lag, 5x20mm

## EMC TEST LEVELS, COMPLIANCE LEVELS, AND ENVIRONMENTAL GUIDANCE

| Guidance and Manufacturer's Declaration: Electromagnetic Immunity | | | |
|---|---|---|---|
| The Alair® RF Controller Model ATS 200 is intended for use in the electromagnetic environment specified below. The user of the Controller should assure that it is used in such an environment. | | | |
| **Immunity Test** | **IEC 60601 Test Level** | **Compliance Level** | **EMC Environmental Guidance** |
| Electrostatic discharge (ESD)<br><br>IEC 61000-4-2 | ±6kV contact<br><br>±8 kV air | ±6kV contact<br><br>±8 kV air | Floors should be wood, concrete or ceramic tile. If floors are covered with synthetic material, the relative humidity should be at least 30%. |
| Electrical fast transient/burst<br><br>IEC 61000-4-4 | ±2 kV for power supply lines<br><br>±1 kV for input/ output lines | ±2 kV for power supply lines<br><br>NA - no input/ output lines | Mains power quality should be that of a typical commercial or hospital environment. |
| Surge<br><br>IEC 61000-4-5 | ±1 kV differential mode<br><br>±2 kV common mode | ±1 kV differential mode<br><br>±2 kV common mode | Mains power quality should be that of a typical commercial or hospital environment. |
| Voltage dips, short interruptions and voltage variations on power supply input lines<br><br>IEC 61000-4-11 | <5 % $U_T$ (>95 % dip in $U_T$) for 0,5 cycle<br><br>40 % $U_T$ (60 % dip in $U_T$) for 5 cycles<br><br>70 % $U_T$ (30 % dip in $U_T$) for 25 cycles<br><br><5 % $U_T$ (>95 % dip in $U_T$) for 5 sec | <5 % $U_T$ (>95 % dip in $U_T$) for 0,5 cycle<br><br>40 % $U_T$ (60 % dip in $U_T$) for 5 cycles<br><br>70 % $U_T$ (30 % dip in $U_T$) for 25 cycles<br><br><5 % $U_T$ (>95 % dip in $U_T$) for 5 sec | Mains power quality should be that of a typical commercial or hospital environment. If the user of the Controller requires continued operation during power interruptions, it is recommended that the Controller be powered from an uninterruptible power supply or a battery. |
| Power frequency (50/60 Hz) magnetic field<br><br>IEC 61000-4-8 | 3 A/m | 3 A/m | Power frequency magnetic fields should be at levels characteristic of a typical location in a typical commercial or hospital environment. |
| NOTE $U_T$ is the a.c. mains voltage prior to application of the test level. | | | |

**Guidance and Manufacturer's Declaration – Electromagnetic Immunity (continued)**

The Alair® RF Controller Model ATS 200 is intended for use in the electromagnetic environment specified below. The customer or the user of the Controller should assure that it is used in such an environment.

| Immunity Test | IEC 60601 Test Level | Compliance Level | Electromagnetic Environment - Guidance |
|---|---|---|---|
| Conducted RF IEC 61000-4-6 | 3 $V_{rms}$ 150 kHz to 80 MHz | 3 $V_{rms}$ | Portable and mobile RF communications equipment should be used no closer to any part of the Controller, including cables, than the recommended separation distance calculated from the equation applicable to the frequency of the transmitter.<br><br>**Recommended separation distance:**<br><br>$d = [1.17]\sqrt{P}$ MHz to 800 MHz |
| Radiated RF IEC 61000-4-3 | 3 V/m 80 MHz to 2.5 GHz | 3 V/m | $d = [1.17]\sqrt{P}$ MHz to 800 MHz<br><br>$d = [2.33]\sqrt{P}$ MHz to 2.5 GHz<br><br>where *P* is the maximum output power rating of the transmitter in watts (W) according to the transmitter manufacturer and *d* is the recommended separation distance in meters (m).<br><br>Field strengths from fixed RF transmitters, as determined by an electromagnetic site survey,[a] should be less than the compliance level in each frequency range[b].<br><br>Interference may occur in the vicinity of equipment marked with the following symbol:  |

**NOTE 1** At 80 MHz and 800 MHz, the higher frequency range applies.

**NOTE 2** These guidelines may not apply in all situations. Electromagnetic propagation is affected by absorption and reflection from structures, objects and people.

[a] Field strengths from fixed transmitters, such as base stations for radio (cellular/cordless) telephones and land mobile radios, amateur radio, AM and FM radio broadcast and TV broadcast cannot be predicted theoretically with accuracy. To assess the electromagnetic environment due to fixed RF transmitters, an electromagnetic site survey should be considered. If the measured field strength in the location in which the Alair® RF Controller Model ATS 200 or any of its components or accessories are used exceeds the applicable RF compliance level above, the Controller should be observed to verify normal operation. If abnormal performance is observed, additional measures may be necessary, such as reorienting or relocating components or accessories or the entire Alair® Bronchial Thermoplasty System.

[b] Over the frequency range 150 kHz to 80 MHz, field strengths should be less than 3 V/m.

| Guidance and Manufacturer's Declaration: Electromagnetic Emissions | | |
|---|---|---|
| The Controller is intended for use in the electromagnetic environment specified below. The customer or the user of the Controller should assure that it is used in such an environment. | | |
| **Emissions Test** | **Compliance Level** | **EMC Environmental Guidance** |
| RF Emissions<br>CISPR 11 | Group 2 | The Controller must emit electromagnetic energy in order to perform its intended function. Nearby electronic equipment may be affected. |
| RF Emissions<br>CISPR 11 | Class B | The Controller is suitable for use in all establishments, including domestic establishments and those directly connected to the public low-voltage power supply network that supplies buildings used for domestic purposes. |
| Harmonic emissions<br>IEC 61000-3-2 | Class B | |
| Voltage fluctuations / flicker emissions<br>IEC 61000-3-3 | Complies | |

## IEC Recommended Separation of RF Communication Equipment

**Recommended separation distances between portable and mobile RF communications equipment and the Alair® RF Controller Model ATS 200 System**

The Alair® RF Controller Model ATS 200 is intended for use in an electromagnetic environment in which radiated RF disturbances are controlled. The customer or the user of the Controller can help prevent electromagnetic interference by maintaining a minimum distance between portable and mobile RF communications equipment (transmitters) and the Controller as recommended below, according to the maximum output power of the communications equipment.

| Rated maximum output power of transmitter W | Separation distance according to frequency of transmitter M | | |
|---|---|---|---|
| | 150 kHz to 80 MHz $d = [\frac{3.5}{V_1}]\sqrt{P}$ | 80 MHz to 800 MHz $d = [\frac{3.5}{E_1}]\sqrt{P}$ | 800 MHz to 2.5 GHz $d = [\frac{7}{E_1}]\sqrt{P}$ |
| 0.01 | 0.12 | 0.12 | 0.23 |
| 0.1 | 0.37 | 0.37 | 0.74 |
| 1 | 1.17 | 1.17 | 2.33 |
| 10 | 3.69 | 3.69 | 7.38 |
| 100 | 11.67 | 11.67 | 23.34 |

For transmitters rated at a maximum output power not listed above, the recommended separation distance d in meters (m) can be determined using the equation applicable to the frequency of the transmitter, where P is the maximum output power rating of the transmitter in watts (W) according to the transmitter manufacturer.

**NOTE 1** At 80 MHz and 800 MHz, the separation distance for the higher frequency range applies.

**NOTE 2** These guidelines may not apply in all situations. Electromagnetic propagation is affected by absorption and reflection from structures, objects and people.

**NOTE 3** $V_1$ is 3 $V_{rms}$ per the conducted emissions compliance level indicated in the table above

**NOTE 4** $E_1$ is 3 V/m per the radiated emissions compliance level indicated in the table above

**CUSTOMER SERVICE**
All questions or concerns related to the Controller should be directed to Asthmatx Customer Service or an authorized Asthmatx representative. No product may be returned without prior authorization. Please contact Asthmatx Customer Service or an authorized Asthmatx representative for a Return Material Authorization (RMA) number. See "Contact Us".

**PRODUCT WARRANTIES**
This section applies only to the purchase of the Alair® Controller.

Asthmatx warrants that for a period of twelve (12) months from the Controller delivery date or the last date of execution of your sale agreement if Customer is already in receipt of Controller (the "Warranty Period"), the Controller sold hereunder will be free from material defects in materials, function and workmanship and will conform to Asthmatx's specifications in effect as of the date of manufacture. This limited warranty extends only to Customer as original purchaser unless otherwise agreed upon in writing by Asthmatx.

If during the Warranty Period: (i) Asthmatx is notified promptly upon discovery of any defect in the Controller (ii) such Controller is returned to Asthmatx's designated facility with the prior approval of Asthmatx with a valid Returned Material Authorization (RMA) number, and (iii) Asthmatx's inspections and tests determine that the Controller is indeed defective and the Controller has not been subjected to any of the conditions set forth below under Warranty Exclusions, then, as Customer's sole remedy and Asthmatx's sole obligation under the foregoing warranty, Asthmatx will, at Asthmatx's option, repair or replace without charge the defective Controller.

**WARRANTY EXCLUSIONS**
**This section applies only to the purchase of the Alair® Controller.**

**THE WARRANTY SET FORTH IN "PRODUCT WARRANTIES" SHALL NOT APPLY IF THE DEFECTIVE ALAIR® CONTROLLER (A) HAS BEEN SUBJECTED TO ABUSE, MISUSE, NEGLECT, NEGLIGENCE, ACCIDENT, IMPROPER TESTING, IMPROPER INSTALLATION, IMPROPER STORAGE, IMPROPER HANDLING OR USE CONTRARY TO ANY DOCUMENTATION OR INSTRUCTIONS ISSUED BY ASTHMATX, (B) HAS BEEN REPAIRED OR ALTERED, (C) HAS NOT BEEN INSTALLED, OPERATED, AND MAINTAINED IN ACCORDANCE WITH THE DOCUMENTATION OR OPERATED OUTSIDE OF THE ENVIRONMENTAL SPECIFICATIONS FOR THE ALAIR® CONTROLLER; (D) HAS FAILED DUE TO AN ACT OF NATURE, INCLUDING BUT NOT LIMITED TO FIRE, FLOOD, TORNADO, EARTHQUAKE, HURRICANE OR LIGHTNING OR (E) HAS BEEN USED WITH ANY DEVICES, ACCESSORIES OR EQUIPMENT NOT MANUFACTURED BY OR APPROVED BY ASTHMATX FOR THE ALAIR® SYSTEM. IN ADDITION, THE FOREGOING WARRANTY SHALL NOT APPLY TO ALAIR® CONTROLLER(S) (A) MARKED OR IDENTIFIED AS "EVALUATION" OR "DEMONSTRATION" OR "NOT FOR HUMAN USE" OR (B) LOANED OR PROVIDED TO CUSTOMER AT NO COST.**

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## SYMBOL LEGEND

| | |
|---|---|
|  | Model Number |
|  | Defibrillation-Proof Type CF Applied Part |
|  | Neutral Electrode Isolated from Earth at High Frequencies |
|  | Caution |
|  | Alternating Current |
|  | Equipotentiality Connector |
|  | Fuses |
|  | Power Off, Disconnected from the Mains |
|  | Power On, Connected to the Mains |
|  | Catheter |
|  | Patient Return Electrode |
|  | Transmits and Accepts Radiofrequency Signals |

| | |
|---|---|
|  | Footswitch |
|  | Serial Communication Port |
| SW1 | Program Memory Enable, for Use Only by Qualified Service Personnel |
|  | Manufacturer Name |
|  | Underwriters Laboratory Safety Certification Mark |
|  | WEEE- Waste of electrical and electronic equipment |
|  Only | For sale by or on order of a physician only |

## TRADEMARKS, PATENTS, AND COPYRIGHT

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www.asthmatx.com

PN 11506 Rev E
April 2010

# Appendix H

FDA Executive Summary

P080032

Asthmatx, Incorporated

Alair® Bronchial Thermoplasty System

Anesthesiology and Respiratory Therapy Devices Panel

October 28, 2009

## TABLE OF CONTENTS

## Introduction

The subject of this Executive Summary is the premarket approval application (PMA# P080032) for a first-of-a-kind device for the treatment of severe persistent asthma in adults, the Alair® Bronchial Thermoplasty System. The Alair system delivers thermal radio frequency energy to bronchial airways using a catheter-based system delivered through a bronchoscope. The intent of the treatment is to reduce airway smooth muscle mass in order to reduce airway narrowing and improve asthma-related quality of life and reduce the frequency or severity of asthma symptoms.

This PMA is under review in the Anesthesiology and Respiratory Devices Branch of the Division of Anesthesiology, General Hospital, Infection Control, and Dental Devices at the Center for Devices and Radiological Health of the Food and Drug Administration. Your time and effort in review of this application are greatly appreciated.

## 1. Rationale for Presentation to Panel

The Alair Bronchial Thermoplasty System is a novel treatment of severe persistent asthma in adults using radiofrequency technology.

FDA is seeking input from the panel regarding the following:

1. The interpretation of the effectiveness results;

2. Whether the totality of the data provide a reasonable assurance that the device is safe and effective for its intended use; and

3. Discussion of goals and endpoints for follow-up of premarket and post-market cohorts.

## 2. Device Description and Background

### 2.1. Indications for Use

The Alair System is indicated for the treatment of severe persistent asthma in patients 18 years and older.

### 2.2. Device Description

The Alair System consists of an Alair Catheter, an Alair Radio frequency (RF) Controller, a commercially available patient return electrode (purchased by the user), and a commercially available footswitch to operate the controller unit, as shown in Figure 1.

The catheter, provided sterile for single-use, has a 1.3 mm flexible shaft that is used to feed a basket-shaped electrode array into the lower airways through a bronchoscope. Opening and closing of the electrode array is controlled from an attached handle at the proximal end of the catheter.

The controller is a non-sterile, reusable unit that provides temperature-controlled delivery of RF energy to the Alair Catheter. The power output is automatically adjusted in response to catheter temperature according to a temperature control algorithm. The controller unit continuously monitors RF output power, load impedance, and RF treatment duration. Temperature set point, power limit, maximum energy delivery and delivery time are not user adjustable, but are configured in the RF Controller software incorporating safety algorithms to limit maximum tissue temperature to 65°C over a maximum of 10 seconds with total energy delivery not to exceed 120 Joules. The controller automatically performs a number of tests to verify normal circuitry function at startup. A short feedback tone is emitted when RF energy is delivered to the catheter and a short dual tone is emitted every two seconds thereafter until RF delivery is discontinued. If a safety issue is detected, the controller enters a fault state and disables RF activation.

A commercially available patient return electrode is used to complete the return path of the electrical circuit to the RF controller. This electrode is not supplied with the Alair System, but Asthmatx includes recommendations for selection of an appropriate electrode in the User Manual. A foot switch is provided to connect to the RF controller to turn the RF output on and off.

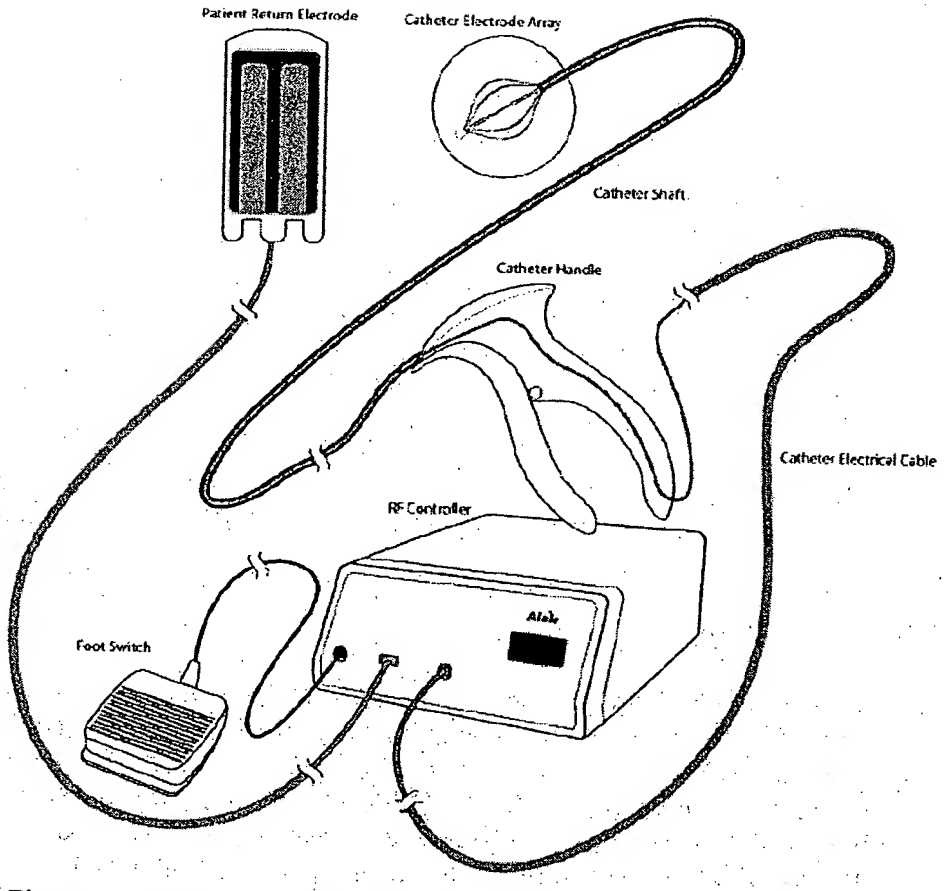



Figure 1. Components of the Alair Bronchial Thermoplasty System

## 2.3.Procedure Description

Treatment with the Alair System is an out-patient procedure. The catheter is inserted through a bronchoscope with the patient under conscious sedation. The catheter is first positioned in the most distal targeted airway and the electrode array is extended. Once the array basket is in contact with the airway wall, RF energy is delivered through the catheter to heat tissue to 65°C over the 5 mm area of exposed (uninsulated) electrode wire. Complete treatment of any given airway requires delivery of RF energy along the entire accessible length of the airway, so the catheter must be repositioned and the electrode redeployed several times. Treatment in the pivotal trial was staged in three sessions: (1) lower lobe of one lung; (2) lower lobe of the opposite lung; (3) both upper lobes. Treatments were scheduled at least three weeks apart. Patients were monitored after treatment until lung function, measured by the forced vital capacity in 1 second ($FEV_1$), returns to 80% of the pre-procedure level

### 2.4.Treatment and Pivotal Trial Rationale

Asthma is a disease which involves airway lining cells and airway smooth muscle with inflammation and airway constriction. Current medical treatment targets both inflammation and bronchospasm (muscular narrowing of the airway). Despite currently optimal medical treatment, some patients with asthma remain symptomatic with frequent exacerbations, often referred to as asthma attacks.

The rationale for bronchial thermoplasty as a treatment for asthma has two components. One component is the theory that reducing airway smooth muscle mass will reduce airway responsiveness and the ability to achieve pathological bronchoconstriction. The second component is the theory that reducing airway smooth muscle mass will not be harmful.

The applicant also conducted preliminary clinical studies of bronchial thermoplasty using medical therapy alone as a control (see Section 5. Prior and Ongoing Clinical Trials).

### 2.5.Regulatory History

The pivotal trial (AIR2) was conducted under Investigational Device Exemption (IDE) #G050082, which received conditional approval on July 21, 2005, and final approval on November 29, 2005. The premarket approval application (PMA) was received in three modules (#M070003/M001, #M070003/M002, and #M070003/M003). The first two modules contained material related to the device and preclinical testing. The third module is the subject of this PMA. It was received by FDA on December 30, 2008 and assigned to the Anesthesiology and Respiratory Devices Branch of the Division of Anesthesiology, General Hospital, Infection Control, and Dental Devices for review under PMA# P080032. Eight amendments were subsequently received in response to FDA questions.

## 3. Preclinical Study Information

The applicant conducted *in vitro* and *in vivo* performance studies of the Alair Bronchial Thermoplasty System. Test results demonstrated that the device is compliant with FDA-recognized international standards for biocompatibility. Bench testing has been performed to evaluate the ability of the device to function correctly, including accurate delivery of thermal energy and appropriate temperature sensitivity. Software that controls the delivery of the thermal energy and prevents delivery at unsafe temperatures has undergone appropriate validation testing. Packaging, shelf life, and sterilization validation testing is incomplete; however, FDA is working interactively with the applicant to resolve these questions. FDA does not believe that these open issues require consideration by the Anesthesiology and Respiratory Therapy Devices Panel.

## 4. Clinical Studies

### 4.1. Pivotal Trial Study (AIR2) Description

Study Design

The AIR2 pivotal trial is a multicenter, randomized, double blinded, sham-controlled clinical trial to demonstrate the safety and effectiveness of the Alair System in patients with severe persistent asthma defined by the presence of persistent symptoms despite conventional medical management with high dose inhaled corticosteroids (ICS) and long-acting $\beta_2$-agonists (LABA). The definition of severe persistent asthma conformed to the GINA 2002 standard (www.ginasthma.com/Guidelineitem.asp?l1=2&intId=82).

Sample Size

The AIR2 pivotal trial was approved for an enrollment of up to 300 patients, including treatment and control. The study was planned to accrue 250 patients to assure a minimum of 225 evaluable patients. A total of 297 patients were randomized at 30 sites (15 US and 15 outside the US (OUS)) with 196 patients randomized to the Alair treatment group and 101 patients to the Sham group. This population represents the main dataset of this PMA application.

Major Inclusion Criteria

(1) Age 18-65 years
(2) Asthma requiring ICS >1000µg/day beclomethasone or equivalent and LABA at least 100µg/day salmeterol or equivalent
(3) Other asthma medication allowed; Oral corticosteroids allowed at ≤ 10 mg/day or 20 mg every other day
(4) Pre-bronchodilator $FEV_1 \geq 60\%$ predicted after baseline stabilization
(4) Baseline Asthma Quality of Life Questionnaire (AQLQ) score ≤ 6.25
(5) Positive bronchial provocation test
(6) At least 2 days of asthma symptoms during a 4-week Baseline Diary Phase
(7) Non-smoker for > 1 year

Major Exclusion Criteria

(1) Use of ≥ 8 puffs/day of short acting rescue medication or 4 puff/day of LABA
(2) 3 or more hospitalizations for asthma in the past year or a history of life-threatening asthma within the past 2 years
(3) More than 4 pulses of oral corticosteroids in the past year
(4) Recurrent lower respiratory tract infections requiring antibiotics
(5) Significant co-morbid disease

Randomization

A 2:1 randomization scheme was used. Randomization was stratified by investigator, symptom-free days (0, 1-40, >40), AQLQ (<4.75, 4.75 to 5.75, >5.75).

Protocol Treatment and Follow-Up

All patients underwent a 4-week Baseline Phase. After this period, patients were randomized at the time of the first procedure to Alair treatment or Sham control. All patients underwent three bronchoscopic procedures, each separated by approximately 3 weeks. The period from the first treatment to 6 weeks after the last treatment is referred to as the Treatment Phase. The Post-Treatment Phase lasted from the end of the Treatment Phase to 12 months. Two 12-month follow-ups occurred, Part 1 and Part 2. After the Part 1 follow-up, patients discontinued LABA treatment. The second 12-month follow-up (Part 2) occurred 2 weeks after the first 12-month follow-up after patients had been off LABA treatment for 2 weeks. The study blind was broken after the 12-month Part 2 visit. Sham treated patients were exited from the study and Alair treated patients entered a Post-Study Safety Follow-up Phase to last 5 years from the beginning of the AIR2 trial. A subset of the first 150 patients enrolled (100 Alair and 50 Sham) were assigned to have high resolution chest CT scans (HRCT) at baseline, 12 months, 3 years, and 5 years.

Blinding

The sham bronchoscopic procedure was performed to carefully mimic the Alair treatment procedure in equipment, auditory cues, and duration of treatments. At each investigative site, unblinded personnel (Bronchoscopy Team) performed the treatment and sham procedures. All post-procedure care for Treatment and Post-Treatment Phases was provided by a blinded Assessment Team. In particular, post-procedure monitoring and care prior to discharge was performed by the blinded Assessment Team to ensure that clinical decisions regarding post-procedure adverse events were not biased or likely to break the study blind.

## 4.2. AIR2 Study Endpoints

Primary Effectiveness Endpoint

The primary effectiveness endpoint was the difference between the Alair and Sham groups in the change in the Asthma Quality of Life Questionnaire (AQLQ) score from Baseline to the average of the 6, 9, and 12 month follow-up visits, termed the integrated AQLQ score.

The AQLQ produces a numeric score on a 7-point scale (see Appendix 2). A higher score represents a better quality of life with respect to asthma symptoms. The minimal clinically important difference in MCID score was prespecified as 0.5 between treatment groups.

Secondary Effectiveness Endpoints

Secondary effectiveness endpoints were the differences between Alair and Sham groups from baseline to 6 and 12 month follow-up visits in the following parameters:

- Absolute change from baseline in percent symptom-free days
- Total symptom score
- Morning peak expiratory flow rate (amPEF)

- AQLQ scores for individual visits at 6, 9, and 12 months
- AQLQ Individual Domain scores
- Asthma Control Questionnaire (ACQ) score
- Number of puffs of rescue medication used
- Percent of days rescue medication was used
- $FEV_1$

Other Effectiveness Variables

Differences between Alair and Sham groups from baseline to 6 and 12 months were also assessed in the following additional parameters:

- Evening peak expiratory flow rate (pmPEF)
- Forced vital capacity (FVC)
- Methacholine $PC_{20}$
- Nighttime awakenings for asthma
- Severe asthma exacerbations (Busse W, et al. *J Allergy Clin Immunol* 2001;108:184-190)
- Mild asthma exacerbations (Pauwels R, et al. *N Engl J Med* 1997;337:1405-1411)
- Change in maintenance asthma medications
- Percent of days lost from work, school, or other daily activities due to worsening asthma
- Number of patients that withdrew from the study due to worsening asthma
- Change between ON-LABA at baseline and OFF-LABA at 12 months in key parameters.

Safety

Safety analyses included:

- Short-term safety – adverse events profile during the Treatment Phase
- Long-term safety – adverse event profile during the Post-Treatment Phase

Additional Safety Analyses

- $FEV_1$ between baseline and follow-up visits
- Unscheduled physician office visits for respiratory symptoms
- Emergency room visits for respiratory symptoms
- Hospitalizations for respiratory symptoms
- Blinded evaluation of HRCT scans.

Brief Statistical Plan

The primary effectiveness endpoint was to be analyzed in the intent-to-treat (ITT) and per-protocol (PP) populations using Bayesian methods. Missing data were to have been be imputed using Bayesian techniques.

The ITT population consisted of all randomized patients who had undergone at least one bronchoscopy. The PP population excluded all patients in the ITT population who met any of the following criteria: missed one or more bronchoscopy, took interfering medication, underwent an interfering treatment, or did not attend one of the 6, 9, or 12 month visits for reasons other than a study-related adverse event.

As a result of two planned interim analyses, the posterior probability of superiority of Alair over Sham for the primary effectiveness endpoint was changed from ≥ 95.0% to ≥96.4% to control the Type I error of the study to be no greater than 0.05. The study was powered to show a statistically significant difference between the study arms. A change in the integrated AQLQ score of 0.5 is considered clinically meaningful.

Bayesian methods were also specified for analysis of the secondary effectiveness endpoints. Missing data would be imputed using the last observation carried forward (LOCF) methods. The target posterior probability of superiority value was ≥ 95.0%. Descriptive statistics were prespecified for the other effectiveness variables and handling of missing data was not described.

The safety analysis is based on the ITT population with prespecified Bayesian methods.

Additional analyses were performed to assess poolability of data and adequacy of the blinding.

### 4.3.AIR2 Pivotal Trial Results – Study Population

Patient Accountability, Protocol Violations, and Missing Data

Of the 297 patients randomized at 30 centers, 9 patients withdrew consent prior to the first bronchoscopy (6 Alair and 3 Control) resulting in 288 patients in the ITT population. 10 patients (9 Alair, 1 Control) were lost to follow-up. 278 patients (96.5%) completed the 12-month Part 1 evaluation. 268 patients constituted the PP population. No patients were withdrawn due to worsening asthma.

Table 1. Patient Disposition

| | Alair | Sham |
|---|---|---|
| Number of Patients Randomized | 196 | 101 |
| Number of Patients Receiving ≥ 1 Bronchoscopy (ITT) | 190 | 98 |
| Number of Patients completed 12-month part 1 visit | 181 | 97 |
| Reasons for Premature Study Discontinuation* | | |
| Non-medical voluntary withdrawal | 4 | 2 |
| Medical voluntary withdrawal | 2 | 2 |
| Withdrawn by investigator | 6 | 0 |
| Lost to follow-up | 6 | 1 |
| Death (not study related) | 1 | 0 |

*Note: Patients may have had more than one reason for discontinuation.
Reproduced from PMA P080032 Vol, Table 3, , page 168

A total of 212 major and 689 minor protocol violations occurred. Of the 212 major violations, 122 were due to bronchoscopy medications not per protocol; 51 patients

did not meet all inclusion/exclusion criteria; and 22 were given the wrong version of the consent form. Minor violations were mostly due to missed visits or visits outside of protocol windows. 6.6% of the primary effectiveness endpoint assessment visits (critical visits) occurred outside of the protocol window.

Patient Demographics

There were no significant differences in demographics and clinical characteristics between the Alair and Sham groups. Mean baseline AQLQ for the Alair group was 4.30 ± 1.17 and for the Sham group the mean was 4.32 ± 1.21. There was also no significant change in asthma maintenance medications during the study in either the Alair or the Sham arms.

By entry criteria, all patients met the definition of severe persistent asthma (GINA 2002). The applicant has also provided baseline information categorizing patients by asthma control according to 2007 National Asthma Education and Prevention Program (NAEPP) (www.nhlbi.nih.gov/about/naepp) to provide an additional clinical perspective on the patient population. Approximately 30% of patients were "not well controlled" and 70% were "poorly controlled."

Data Pooling and Analyses by Site

In the pivotal trial (IDE) protocol the applicant planned to use a Bayesian hierarchical model to address the existence and amount of heterogeneity across sites. In this PMA, site-to-site variability with respect to the primary effectiveness endpoint was assessed using classical ANCOVA modeling with the following factors: treatment, center, treatment by center interaction, and the baseline AQLQ as a covariate. The p-value for the interaction effect is 0.107. Due to the large number of sites relative to the number of patients and the 2:1 randomization ratio, sample sizes at each site were not large enough to draw any conclusions as to whether the effectiveness of the treatment varies from site to site, although regional (as opposed to site) differences were observed with respect to the primary outcome variable. The applicant pooled all the data for the statistical analyses.

## 4.4. AIR2 Pivotal Trial Results – Effectiveness

Primary Effectiveness Endpoint

The results for the ITT and PP populations are shown in Table 2. Credible intervals (CI) are provided to aid in the interpretation of the size of the differences between groups. Both arms showed clinically significant improvement (>1.0), which may suggest a placebo effect. Table 2 shows the differences in the means between the groups.

Table 2. Primary Effectiveness Results[#] – Differences in Means

| Population (Number of Patients) | Bayesian Estimate of Difference Between Groups | 95% CI (Alair-Sham) | Posterior Probability of Superiority (Alair > Sham) (Success rule ≥ 96.4%) |
|---|---|---|---|
| **ITT**<br>Alair N= 190<br>Sham N= 98 | 0.210 | (-0.025, 0.445) | 96.0% |
| **PP**<br>Alair N= 173<br>Sham N= 95 | 0.244 | (0.009, 0.478) | 97.9% |

# Integrated AQLQ Score: Average of the 6-, 9-, and 12-Month scores
Reproduced from P080032/A08 Table 7, Table 8, page 27, 29

For the prespecified primary effectiveness analysis of the integrated AQLQ change from baseline in the ITT population, the posterior probability of superiority is 96.0%, which is slightly smaller than the prespecified success criteria of 96.4%. The 95% credible interval from the primary analysis is (-0.025, 0.445). For both populations, the lower limits of 95% credible intervals are very close to zero and the upper limits are slightly less than 0.5, the MCID.

Regional Differences in Primary Effectiveness Endpoint

The applicant also provided an analysis of the primary effectiveness outcome by region (US versus Brazil versus other OUS sites). Although all sites followed the same protocol with uniform inclusion and exclusion criteria and uniform monitoring, some regional differences in outcomes were noted. US patients accounted for 30% of randomized patients and showed the largest clinical improvement in integrated AQLQ score for the Alair group compared to the Sham (0.630), while the Brazilian patients did not show improvement compared to the Sham (-0.213), as shown in Table 3.

Table 3. Regional Analysis of AQLQ (ITT)

| Population | Change in AQLQ Score from Baseline to Integrated Score - LOCF | | Bayesian Estimate of Difference Between Groups |
|---|---|---|---|
| | Alair (N) | Sham (N) | |
| US | 1.67 ± 1.13 (59) | 1.13 ± 1.17 (29) | 0.630 |
| Other OUS | 1.13 ± 1.01 (76) | 0.84 ± 1.04 (40) | 0.226 |
| Brazil | 1.32 ± 1.11 (55) | 1.63 ± 1.41 (29) | -0.213 |

Reproduced from P080032/A08 Table 16, page 43

Some other notable regional differences may be considered in evaluating these results:

- The six largest sites accounted for 48% of the ITT cases and 5 of the 6 sites were OUS.

- Seven sites, all OUS and accounting for 43% of the ITT cases, had prior Alair

experience from earlier clinical trials. Alair patients at sites with prior Alair experience did not, however, have improved outcomes with respect to the AQLQ over Sham control patients.

• Free maintenance asthma medication was provided to all study participants at Brazilian sites through the entire study period. This distribution was done for socioeconomic reasons to assure compliance with maintenance medications, but may have potentially influenced outcomes.

AQLQ Within-Patient Changes (Post-hoc Analyses)

The applicant provided post-hoc responder analyses of the primary effectiveness endpoint. A responder analysis of the ITT and PP populations is shown in Table 4. A responder is defined as a patient who shows a change in AQLQ score from baseline of $\geq 0.5$ units. A net responder analysis, combining patients who improved by 0.5 units and patients who deteriorated by 0.5 units, is shown Table 5 for the ITT and PP populations.

Table 4. Responder Analysis for ITT and PP Populations

| Population | % Patients (Number of Patients) Achieving a Change in Integrated AQLQ Score of ≥0.5 | | Difference |
|---|---|---|---|
| | Alair | Sham | |
| ITT | 78.9% (150/190) | 64.3% (63/98) | 14.6% |
| PP | 80.9% (140/173) | 63.2% (60/95) | 17.7% |

Reproduced from P080032/A08 Table 10, page 32

Table 5. Analysis of "Net-Benefits"

| Population | (% of Patients with AQLQ Change of ≥0.5) – (% of Patients with AQLQ Change of ≤ -0.5) (Number of patients) | | Difference |
|---|---|---|---|
| | Alair | Sham | |
| ITT | 76.3% (145/190) | 57.1% (56/98) | 19.2% |
| PP | 80.9% (135/173) | 55.8% (53/95) | 22.2% |

Reproduced from P080032/A08 Table 51, page 120

Secondary Effectiveness Endpoints

Secondary endpoints, with the exception of $FEV_1$, tended to favor the Alair treatment (Table 6). It should be noted that the applicant considers the $FEV_1$ as a safety index and views the lack of deterioration in $FEV_1$ as evidence of device safety.

Table 6. Secondary Effectiveness Endpoints

| Parameter | Mean (LOCF) Alair (N=190) | Sham (N=98) |
|---|---|---|
| AQLQ Symptoms Domain Score | 1.27 | 1.10 |
| AQLQ Activity Limitations Domain Score | 1.24 | 1.07 |
| AQLQ Emotional Functions Domain Score | 1.70 | 1.39 |
| AQLQ Environmental Stimuli Domain Score | 1.48 | 1.29 |
| Pre-BD FEV1 (% Predicted) (Percent change) | -1.4 | -0.1 |
| Post-BD FEV1 (% Predicted) (Percent change) | -2.8 | -2.4 |
| Total Symptom Score | -1.7 | -1.6 |
| % Symptom-Free Days | 24.4 | 21.0 |
| Rescue Medication Use (puffs/7 days) | -6.0 | -4.3 |
| Percent Days Rescue Medication Used | -24.0 | -22.0 |
| ACQ Score | -0.82 | -0.77 |
| amPEF (L/min) | 27.8 | 22.3 |

Reproduced from P080032/A08 Table 11, page 33

Other Effectiveness Variables

Differences were observed in the following endpoints (Table 7): rates of severe exacerbations requiring corticosteroids, proportions of patients with severe exacerbations requiring corticosteroids, number of days lost from work/school/other activities due to respiratory symptoms, emergency room visits for respiratory symptoms, and asthma (multiple symptoms). The first three endpoints were prespecified in the IDE protocol (#G050082) as other variables for which descriptive analyses were proposed. Emergency room visits for respiratory symptoms was a prespecified safety endpoint and asthma (multiple symptoms) was a prespecified adverse event. The applicant notes that these variables correspond to the goals of asthma management recommended in the 2007 NAEPP guidelines which were published after the initiation of this pivotal trial, which began in 2005.

Table 7. Other Endpoints in Support of Effectiveness

| | Alair (N=190) | Sham (N=98) |
|---|---|---|
| 1. Rate of Severe Exacerbations (steroid exacerbations) (Events/ patient/ Year) | 0.48 | 0.70 |
| 2. Proportions of patients with Severe Exacerbations requiring steroids | 26.3% | 39.8% |
| 3. Days lost from work, school, or other daily activities due to asthma symptoms (Days/Patient/Year) | 1.3 | 3.9 |
| 4. Emergency Room visits for respiratory symptoms (Events/patient/year) | 0.07 | 0.43 |
| 5. Asthma (multiple symptoms) AE/patient/week | 0.009 | 0.014 |

Reproduced from P080032/A08 Table 14, page 37 and P080032/A08 Table 6, page 26

Blinding Assessment

No patients or Assessment Team members were inadvertently unblinded. For the Assessment Team, the largest percentage of responses were "I have no idea" at all time points.

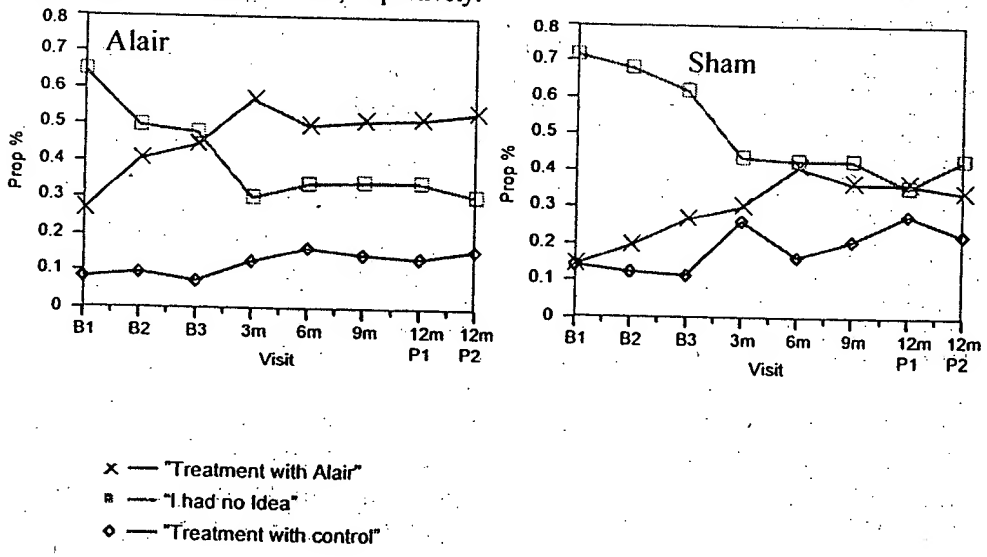
For both the Alair and Sham group patients, the proportion who reported they received the actual treatment generally increased from the first Bronchoscopy to the last blinding assessment (12 month part 2 visit). Additionally, for both the Alair and Sham group, the proportion of patients who reported they received the sham treatment also increased over time with small fluctuations (Table 8 and Figure 2). On average, 17% more Alair patients reported "Treatment with Alair" than the Sham patients from the first bronchoscopy (Bron1) through the 12-month follow-up and 28% more Alair patients correctly reported their treatment assignment than the Sham patients.

Table 8. Patient blinding responses (%) by visit and treatment group

| | "Treatment with Alair" | | "Treatment with Control" | | " I have no idea " | |
|---|---|---|---|---|---|---|
| Visit | Alair (%) | Sham (%) | Alair (%) | Sham (%) | Alair (%) | Sham (%) |
| Bron1 | 0.27 | 0.14 | 0.08 | 0.14 | 0.65 | 0.71 |
| Bron2 | 0.41 | 0.20 | 0.10 | 0.12 | 0.50 | 0.68 |
| Bron3 | 0.44 | 0.27 | 0.08 | 0.11 | 0.48 | 0.62 |
| 3-mo | 0.57 | 0.30 | 0.13 | 0.26 | 0.30 | 0.44 |
| 6-mo | 0.50 | 0.41 | 0.16 | 0.16 | 0.34 | 0.43 |
| 9-mo | 0.51 | 0.36 | 0.15 | 0.21 | 0.34 | 0.43 |
| 12-mo P1 | 0.52 | 0.36 | 0.14 | 0.28 | 0.34 | 0.35 |
| 12-mo P2 | 0.53 | 0.34 | 0.16 | 0.23 | 0.31 | 0.43 |

Source: P080032, Vol 1., Table 12, page 188

**Figure 2. Patient Blinding Assessment (Left: Alair; Right: Sham).** The horizontal axis is the visits at which the blinding assessment was conducted. The vertical axis represents the proportions of patients in the Alair and in the Sham group who reported they received the Alair treatment, the Sham treatment and had no idea, respectively.




Source: P080032, Vol 1., Table 12, page 188

## 4.5. AIR2 Pivotal Trial Results – Safety

Respiratory Adverse Events (AE) (Table 9)

Both Alair and Sham patients experienced a large increase in respiratory AEs compared to baseline during the Treatment Phase, but the rates decrease for both groups in the Post-Treatment Phase. The rates during the Treatment Phase are higher in the Alair group than the Sham. The Post-Treatment rate of AEs is slightly lower in the Alair group than the Sham. The rates do not return to baseline for either group, but the applicant notes in explanation that the methods of collection of AEs were different during the baseline and subsequent phases. The diary collection method during the baseline phase may have underestimated AEs compared to the direct questioning during the Treatment and Post-Treatment phases.

Respiratory Serious Adverse Events (SAE) (Table 9)

The rates of SAEs during the Treatment Phase was higher in the Alair group than the Sham group. The rates were comparable during the Post-Treatment Phase.

Table 9. Summary of Respiratory Adverse Events and Serious Adverse Events

| | Baseline | | Treatment Phase | | Post-Treatment Phase | |
|---|---|---|---|---|---|---|
| | Alair | Sham | Alair | Sham | Alair | Sham |
| | (N=190) | (N=98) | (N=190) | (N=98) | (N=187) | (N=98) |
| Respiratory AEs Reported ( Number of patients) | 52 (35) | 21 (19) | 573 (161) | 206 (74) | 345 (130) | 201 (78) |
| **Number of Respiratory AEs/ Patient/Week** | **0.019 ± 0.046** | **0.018 ± 0.046** | **0.202 ± 0.148** | **0.141 ± 0.115** | **0.038 ± 0.039** | **0.042 ± 0.037** |
| Respiratory Serious Adverse Events (Number of patients) | 2 (1) | 0 | 17 (16) | 2 (2) | 6 (6) | 4 (4) |
| **Number of Respiratory SAEs/ Patient/Week** | **0.000 ± 0.005** | **0.000 ±0.000** | **0.007 ± 0.025** | **0.002 ± 0.018** | **0.001 ± 0.004** | **0.001 ± 0.004** |
| "Asthma (multiple symptoms)" Adverse Events Reported (Number of patients) | 13 (12) | 2(2) | 211 (95) | 67 (38) | 87 (51) | 68 (42) |
| **Number of "Asthma (multiple symptoms)" AEs/Patient/Week** | **0.005 ± 0.018** | **0.001 ± 0.011** | **0.073 ± 0.087** | **0.046 ± 0.071** | **0.009 ± 0.018** | **0.014 ± 0.022** |

Reproduced from P080032/A08 Table 5, page 24 and Table 6, page 26

Overall, there were no device or asthma-related deaths and no deterioration in $FEV_1$. The most common AE and SAE in the Treatment Phase was Asthma (multiple symptoms) which occurred in 95/190, 50% of Alair patients and 38/98, 39% of Sham patients. Lower respiratory tract infections occurred in 16/190, 8% of Alair patients and 2/98, 2% of Sham patients.

Hemoptysis occurred in 6 Alair patients (3%). Five of these cases ranged from mild to moderate, self-limited hemoptysis occurring within 2 weeks of the procedure. The sixth case exhibited severe hemoptysis (estimated blood loss 100 ml) which occurred 31 days after the third thermoplasty treatment and required bronchial

artery embolization. Bronchoscopic examination showed bleeding from an area distal to the point at which the bronchoscope could have been deployed.

Additional Safety Endpoints for Respiratory Symptoms

During the Treatment Phase, unscheduled physician office visit and hospitalizations were higher in the Alair group than the Sham group, but lower during the Post-Treatment Phase (Table 10). Emergency room visits were lower in the Alair group than the Sham group in both the Treatment and Post-Treatment Phases (Table 10).

Table 10. Summary of Additional Safety Endpoints for Respiratory Symptoms

| | Treatment Phase | | | | Post-Treatment Phase | | | |
|---|---|---|---|---|---|---|---|---|
| | Alair (N=190) | | Sham (N=98) | | Alair (N=187) | | Sham (N=98) | |
| | No. of events (No. of patients) | No. of Events / Patient | No. of events (No. of patients) | No. of Events / Patient | No. of events (No. of patients) | No. of Events / Patient | No. of events (No. of patients) | No. of Events / Patient |
| Unscheduled Physician Office Visits | 54 (37) | 0.284 | 18 (10) | 0.184 | 46 (32) | 0.242 | 31 (20) | 0.316 |
| Emergency Room Visits | 13 (10) | 0.068 | 10 (3) | 0.102 | 11 (7) | 0.058 | 34 (15) | 0.347 |
| Hospitalization | 19 (16) | 0.100 | 2 (2) | 0.020 | 6 (5) | 0.032 | 12 (4) | 0.122 |

Reproduced from P080032, Vol 1. Table 43-45, page 267-269

HRCT Results

In the 150 patients assigned to HRCT scan examinations, at 1-year, there was no difference in signs of gas trapping or consolidation and there was no evidence of bronchiectasis. A difference was seen in bronchial wall thickening without gas trapping which occurred only in the Sham patients (4%). In addition, the Alair feasibility trial found no evidence of abnormal CT findings in Alair treated patients at 1, 2, 3, 4, or 5 year follow-up (n=16).

## 5. Prior and Ongoing Clinical Trials

Prior clinical trials were conducted feasibility, safety and effectiveness evaluations of the Alair treatment. These trials had different indications for use, different inclusion/exclusion criteria, and different endpoints than the AIR2 trial. Summary results were provided by the applicant as part of this PMA. Safety information from these studies is summarized briefly below.

Feasibility Trial

This trial was a multicenter, single arm study of the Alair treatment in 16 patients with *mild to severe*, stable asthma on maintenance ICS. The purpose was to evaluate safety at 3 months after which patients were followed annually to 5 years. The number of respiratory adverse events/patient remained stable from year 1 to year 5. No abnormalities were observed on yearly HRCT scan through 5 years.

AIR Trial

This trial was a multicenter, randomized, controlled trial comparing Alair to medical therapy alone in *moderate to severe* asthmatics and assessing the ability of patients to withdraw from LABA in the Post-Treatment Phase. A total of 109 patients were involved

– 55 Alair and 54 Control. Enrollment required use of ICS and inhaled LABA and a deterioration of at least -0.5 in the AQLQ score off LABA. The percentage of patients with any respiratory AE was higher in the Alair group during both the Treatment and Post-Treatment Phases (93% Alair vs. 67% Control Treatment; 85% Alair vs. 79% Control at Post-Treatment). No change was seen in $FEV_1$.

AIR Extension Study
70 patients from the AIR Trial (46 Alair, 24 Control) were followed through 3 years. 17 Alair patients have finished the 4 year evaluation. Controls were exited after the 3 year evaluation. The percentage of patients with respiratory AEs in both groups diminished over time as did the number of respiratory AEs per patient. The results were comparable in both arms.

RISA Trial
This trial was a multicenter, randomized, controlled trial of Alair versus medical treatment alone in 15 Alair and 17 Control patients to evaluate safety and possible effectiveness out to 12 months in patients with *severe refractory* asthma. The protocol involved steroid weaning. Respiratory AEs were higher in the Alair group during the treatment phase (9.1 events/patient Alair vs. 3.4 events/patient Control) and decreased during the post-treatment phases to levels comparable to the Control group (5.0 Alair vs. 5.0 Control). $FEV_1$ did not change.

RISA Extension Study
14 Alair patients from the RISA trial will be studied annually to 5 years and have completed the 3 Year visit at the time of the AIR2 PMA. Respiratory AEs dropped from 8.4 per patient at Year 1 to 0.9 and 1.1 at Years 2 and 3 respectively.

## 6. Post-Approval Study Plan

*Note: The inclusion of a Post-Approval Study section in this summary should not be interpreted to imply that FDA has made a decision or is making a recommendation on the approvability of this PMA application. The presence of a post-approval study plan or commitment does not in any way alter the requirement for premarket approval. A recommendation for approval from the Panel must be based on the pre-market data. The premarket data must reach the threshold for providing reasonable assurance of safety and effectiveness before the device can be found approvable and any post-approval study can be considered. This section contains comments regarding potential post-approval studies should the Panel find the device approvable following its deliberations of the premarket data.*

The applicant has proposed the following five post-approval activities (which include two post-approval studies): (1) Physician Training Program; (2) Post-approval Study Follow-up of the AIR2 Alair treated patients (safety and effectiveness data of the Alair group patients through 5 years); (3) AIR Extension Study (ongoing - 41 OUS Alair patients to be evaluated at 4 and 5 years); (4) RISA Extension study (ongoing – 14 OUS Alair patients followed for safety through 5 years); and (5) Alair Post-Marketing Registry (enrollment of

a new cohort for safety data).

The two post-approval studies for the enrollment of a new cohort and the continued follow-up of the premarket cohort (AIR2 Alair patients) are outlined below. In deciding whether these post-approval studies are sufficient, the following points should be considered:

- The duration of follow-up in the AIR2 trial was 12 months. The longer term effects of the treatment on local and adjacent areas of the lower respiratory system and the durability of the treatment effectiveness of the device have not been evaluated beyond 12 months.

- The Alair System is the first bronchoscopic system for the treatment of patients with severe persistent asthma, which means that it has not been evaluated under conditions of normal postmarket use outside the setting of a controlled clinical trial.

- The intended US population made up approximately 30% of the AIR2 enrollment.

### 6.1.5-Year Extended Follow-up of AIR2 Alair Patients

Study Design: The Extended Follow-up study is a multi-center, observational, follow-up study of the pivotal study's Alair treated patients.

Study Hypothesis: The subsequent 12-month follow-up rates (for years 2, 3, 4, and 5 in 12 month periods) for proportions of patients experiencing emergency room visits is non-inferior to the first 12-months which begins 6 weeks after the last Alair treatment. Non-inferiority will be demonstrated if the lower 95% confidence limit of the difference (first 12-month rate minus subsequent 12-month reate) is greater than -20%.

Study Population: The study population will consist of surviving Alair treated patients previously enrolled in the AIR2 trial.

Duration of Follow-up: The duration of follow-up will be 5 years post-treatment.

Effectiveness Endpoints: The primary effectiveness endpoint will be the proportion of patients experiencing ER visits for respiratory symptoms The point estimates and 95% confidence intervals for the endpoint during each of the 12 month periods and the lower 95% confidence limit for the difference of the first 12-month rate minus the subsequent 12-month rate will be provided.

Safety Endpoints: Safety endpoints will be respiratory adverse events and hospitalizations for respiratory symptoms.

### 6.2.Alair Bronchial Thermoplasty System Post-Marketing Registry

Study Objective: The objective of this study is to evaluate the longer-term safety of

the Alair System, and, in particular, asthma-related hospitalizations, in the intended US population.

Study Design: The study is a prospective, open-label, single arm, multi-center observational study to evaluate the longer-term safety of the device in patients with severe persistent asthma in the US.

Study Hypothesis: The one-year rate of hospitalizations will not be greater than the observed rate of 30% in the persistent asthma population in the United States as studied in the Severe Asthma Research Program (SARP) (Moore et al. *J Allerg Clin Immunol* 2007; 119:405-413).

Study Population and Sample Size: The study population will consist of patients who meet the inclusion and exclusion criteria. The applicant plans to enroll a total of 250 patients to achieve 200 evaluable patients assuming a 20% drop-out rate over 5 years in up to 30 US centers. A sample size of 200 patients was calculated by the applicant based on the following parameters:

- The expected rate of respiratory hospitalization in the PAS will be less than that observed in the severe persistent asthma population studied in SARP.
- The observed hospitalization incidence rate over the 12-month period in the SARP population was 30%.

Duration of Follow-up: 5 years post treatment

Study Endpoints: Safety endpoints assessed annually and for which descriptive statistics will be provided include:

- Emergency Room Visits for respiratory symptoms
- Hospitalizations for respiratory symptoms
- Other respiratory AEs
- Maintenance asthma medications
- $FEV_1$ (pre- and post-bronchodilator)

No effectiveness endpoints (durability) were specified in the outline.

## 7. Concluding Remark

This executive summary provides an overview of the data that will be presented to the Advisory Panel at its meeting of October 28, 2009. Specific issues for the Advisory Panel to consider are contained in the Questions to the Advisory Panel document.

## Appendix 1 List of Abbreviations

| | |
|---|---|
| ACQ | Asthma Control Questionnaire |
| AE | Adverse event |
| AIR | Asthma Intervention Research |
| ANCOVA | Analysis of co-variance |
| AQLQ | Asthma Quality of Life Questionnaire |
| CI | Confidence interval or credible interval |
| ER | Emergency room |
| $FEV_1$ | Forced vital capacity in 1 second |
| FVC | Forced vital capacity |
| GINA | Global Initiative for Asthma |
| HRCT | High resolution chest computed tomogram |
| ICS | Inhaled corticosteroid |
| IDE | Investigational device exemption |
| ITT | Intent-to-Treat |
| LABA | Long-acting beta agonist |
| LOCF | Last observation carried forward |
| MCID | Minimal clinically important difference |
| NAEPP | National Asthma Education and Prevention Program |
| OUS | Outside the United States |
| PAS | Post-approval study |
| amPEF | Morning peak expiratory flow |
| pmPEF | Evening peak expiratory flow |
| PMA | Premarket application |
| PP | Per Protocol |
| Pre-BD | Pre-bronchodilator |
| Post-BD | Post-bronchodilator |
| RF | Radiofrequency |
| RISA | Research In Severe Asthma |
| SAE | Serious adverse event |
| US | United States |

## Appendix 2 Asthma Quality of Life Questionnaire (AQLQ) Summary

The Asthma Quality of Life Questionnaire (AQLQ) is an asthma specific quality of life instrument. It may be interviewer or self-administered.

The questionnaire consists of 32 items in four domains:

- activity limitations
- symptoms
- emotional function
- exposure to environmental stimuli.

The AQLQ produces a numeric score on a 7-point scale. A higher score represents a better quality of life with respect to asthma symptoms. The minimal clinically important difference (MCID) is recognized to be 0.5.

The questionnaire is available in many language versions including Czech, Danish, English for Australia, English for New Zealand, English for North America, English for South Africa, English for UK, Finnish, French, French for Quebec, German, Greek, Hebrew, Hungarian, Italian, Norwegian, Polish, Portuguese, Russian, Spanish, Spanish for North America, and Swedish.

References:


1. Juniper EF, et al. Validation of a standardized version of the asthma quality of life questionnaire. *CHEST* 1999;115:1265-1270.
2. Sanjuas C, et al. The quality of life questionnaire with asthma patients: the Spanish version of the Asthma Quality of Life Questionnaire. *Arch Bronchoneumol* 1995;31:219-226.
3. Juniper EF, et al. Determining a minimal important change in a disease-specific quality of life questionnaire. *J Clin Epidemiol* 1994;47:81-87.
4. Juniper EF, et al. Evaluation of impairment of health-related quality of life in asthma: development of a questionnaire for use in clinical trials. *Thorax* 1992;47:76-83.

# Appendix I

# Asthmatx, Inc.

# PANEL PACK
# SPONSOR EXECUTIVE SUMMARY

## P080032

## Bronchial Thermoplasty with the Alair® System

## Sponsor Executive Summary for
## FDA Advisory Panel Meeting

## October 28, 2009

## TABLE OF CONTENTS

## 1.0 Introduction

This Executive Summary provides an overview of the significant unmet clinical need in severe asthma, a description of the Alair® Bronchial Thermoplasty System (hereafter called "The Alair System"), the rationale for the bronchial thermoplasty procedure, and a summary of the safety and effectiveness data obtained through the step-wise preclinical and clinical studies conducted on the Alair System. These data provide valid scientific evidence to establish reasonable assurance of safety and effectiveness to support approval of the Alair System according to its indication for use in adult patients with severe persistent asthma.

The Alair System, a device developed by Asthmatx, Inc. (Sunnyvale, CA), is used to perform bronchial thermoplasty, a procedure for the treatment of severe persistent asthma in adults.

Unlike the currently available therapies for asthma that require ongoing chronic use of medications, treatment with the Alair System does not entail ongoing long-term exposure, but rather is limited to use of the device during acute and discrete procedures.

The preclinical and clinical development of the Alair System has involved a careful and step-wise scientific approach. Four animal studies including a randomized, controlled study were conducted to establish the preclinical proof of principle for the Alair System. A total of 35 dogs have undergone treatment with the Alair System, with long-term follow-up out to a maximum of 3 years. Results from these studies helped define treatment parameters, demonstrated that the procedure is well tolerated, tissue effects are stable by 12 weeks post-treatment, and that the reduction in the airway smooth muscle seen at 12 weeks is maintained over the long-term out to 3 years.

To date, the total clinical experience with the Alair System includes over 800 bronchial thermoplasty procedures in 276 patients performed by physicians at over 30 institutions around the world during the course of 4 clinical trials in patients with asthma. Additionally, through the course of these studies, long-term follow-up data on Alair-treated patients with asthma are available out to 5-years post-treatment. This Executive Summary contains brief summaries of each clinical study including the pivotal IDE study (AIR2 Trial). For more detailed information, more detailed summaries for each clinical report are appended to this Executive Summary (**Appendix A**).

The cumulative results of these 4 trials, 3 of which were randomized, have demonstrated the safety and effectiveness of the Alair System in patients with asthma. The Alair System has been shown to result in a significant improvement in asthma control and in the quality of life of patients with severe asthma. Indeed following review of the data from the pivotal IDE study of the Alair System, Dr. Elizabeth Juniper, the developer of the Asthma Quality of Life Questionnaire (AQLQ) that was used as the primary effectiveness endpoint in the pivotal trial stated, **"I am not aware of any other therapy for severe asthma that has demonstrated this degree of clinically meaningful benefit based on the results of the AQLQ" (see Appendix B).**

All the Principal Investigators who participated in the pivotal AIR2 Trial have provided their independent assessment that the findings in the AIR2 Trial are "meaningful and clinically important outcomes." The Investigators concluded that "the long-term benefits

of this treatment outweigh the observed risks associated with the procedure" and that the "benefits occurred in patients already on treatment with high doses of inhaled corticosteroids and long acting beta-agonists" **(see Appendix C).**

In recognition of the potential significance of the Alair System in the treatment of asthma, the U.S. Food and Drug Administration (FDA) granted Expedited Review Status to the premarket approval application (PMA) for the Alair System (FDA, P080032 October 17, 2008). In granting this Expedited Review status, the FDA cited its potential "to treat asthma, a life-threatening/debilitating disease" and because "The Alair System also offers a breakthrough technology which has the potential to address an unmet clinical need within the asthma population".

## 2.0 Indication for Use

The Alair Bronchial Thermoplasty System is indicated for the treatment of severe persistent asthma in patients 18 years and older.

## 3.0 Severe Asthma: The Unmet Need

### 3.1 Asthma – The Problem

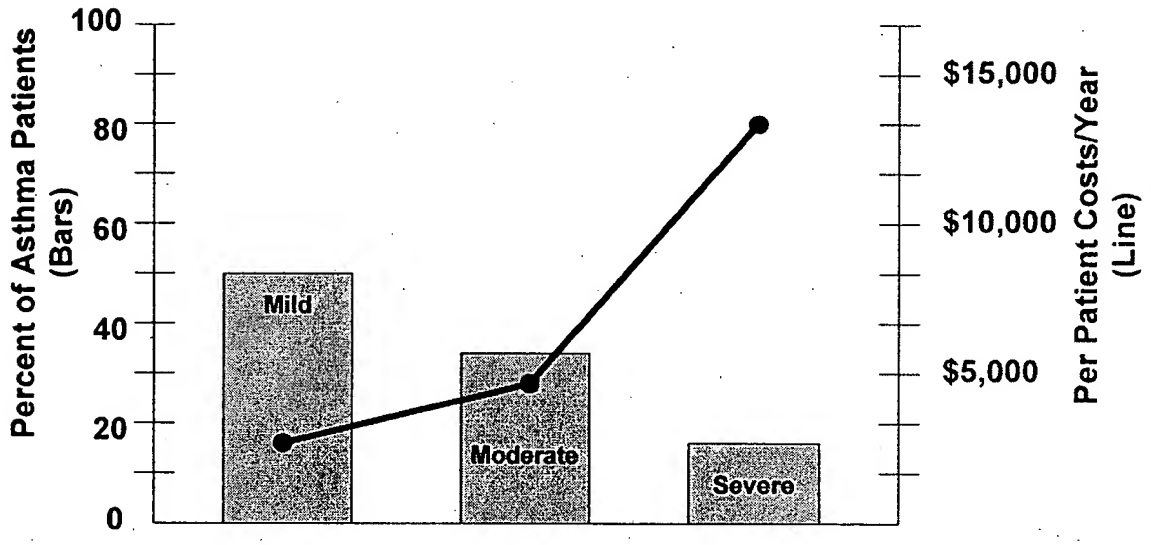
Asthma is a serious public health problem. It has been defined as one of the top five chronic diseases globally, along with heart disease, stroke, cancer, and diabetes. As such, the Centers for Disease Control and Prevention in the United States cited asthma among the top three chronic disease priorities in 2008 along with obesity and diabetes (Centers for Disease Control 2008). The global magnitude of the problem of asthma was highlighted in a recent issue of *The Lancet (September 2008)*, which was entirely devoted to the serious medical problem of asthma.

The current estimate is that 20 million people in the Unites States suffer from asthma. Each year in the United States alone, there are approximately 13.6 million unscheduled physician office visits, 1.8 million emergency room visits, 0.5 million hospitalizations, and 4,000 deaths (NCHS 2005) due to asthma. The estimated annual cost of asthma in the United States is approximately $19.7 billion. This total includes $5 billion in indirect costs, due to more than 14.5 million lost work days, and $14.7 billion in direct costs, such as asthma medications, unscheduled physician office visits, emergency room visits and hospitalizations (American Lung Association 2007).

Ten percent of the more than 20 million Americans with asthma are diagnosed as having severe asthma. This group of severe asthmatics, however, is responsible for a disproportionate share of the morbidity associated with the disease. Consequently, these 10% of patients with the most severe asthma are responsible for the majority of asthma-related healthcare burden, represented by the costs of hospitalizations, ER visits, physician office visits, and use of medications (Cisternas et al, 2003: Figure 1; Dolan et al, 2004). The per-patient cost differences for severe asthma over mild asthma are significant (Cisternas et al, 2003):

- Direct medical care costs are over 3 times greater for patients with severe asthma than for mild asthma;
- Indirect costs (e.g. lost time from work) are 10 times greater for patients with severe asthma than for mild asthma; and
- 17% of the total healthcare costs for asthma are associated with hospital costs for patients with severe asthma compared to only 4% for patients with mild asthma.

Figure 1: Asthma Population and Per Patient Costs by Severity




***Adapted from Cisternas et al. JACI, 2003; 111: 1212-1218***

Because of the significant healthcare concern associated with severe asthma, the National Heart, Lung, and Blood Institute (NHLBI), a division of the National Institutes of Health, has funded the Severe Asthma Research Program (SARP), a unique program focused on severe asthma through collaborative clinical research studies. The NHLBI commitment to SARP over a 5-year period is on the order of $28MM.

Despite regular treatment with high doses of available asthma medications, patients with severe asthma experience frequent and serious symptoms including exacerbations that may be life-threatening and require urgent resuscitative measures including intubation and mechanical ventilation, until the airway obstruction can be relieved. Exacerbations requiring medical intervention result in significant healthcare costs and affect the quality of life for the patient and family (Sears et al, 2008), and increased mortality (Peters et al, 2006). This increased burden of severe asthma reflects the inability of the existing treatment options to adequately control this severe disease.

In summary, there is a significant unmet need for an effective, long-lasting treatment for patients with severe asthma. **The Alair System is a promising new treatment option for patients with severe persistent asthma.** Data from 4 separate clinical studies of bronchial thermoplasty with the Alair System in patients with asthma suggest that this procedure significantly improves asthma control and the related quality of life, the current goals for the management of asthma as revised in 2007 by the National Asthma Education and Prevention Program (NAEPP) Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma, 2007 (NIH Publication No. 07-4051).

The U.S. Food and Drug Administration (FDA) granted Expedited Review Status to the premarket approval application (PMA) for the Alair System (FDA, P080032, October 17, 2008) based on the recognition of the potential significance of the Alair System in the treatment of asthma. In granting this Expedited Review status, the FDA cited its potential "to treat asthma, a life-threatening/debilitating disease" and because "The Alair System also offers a breakthrough technology which has the potential to address an unmet clinical need within the asthma population".

## 3.2 Current Treatment Options for Asthma

Asthma is a common chronic disorder of the airways that is complex and characterized by variable and recurring symptoms, airflow obstruction, bronchial hyper-responsiveness, and an underlying inflammation (GINA 2007). The interaction of these features of asthma determines the clinical manifestations and severity of asthma and the response to treatment (GINA 2007).

Patients and physicians currently manage asthma with a combination of stimulus avoidance and medications, all of which are well documented in the NAEPP Guidelines (2007). Use of medications entails chronic ongoing use of the prescribed medications.

The major groups of currently used asthma medications include:

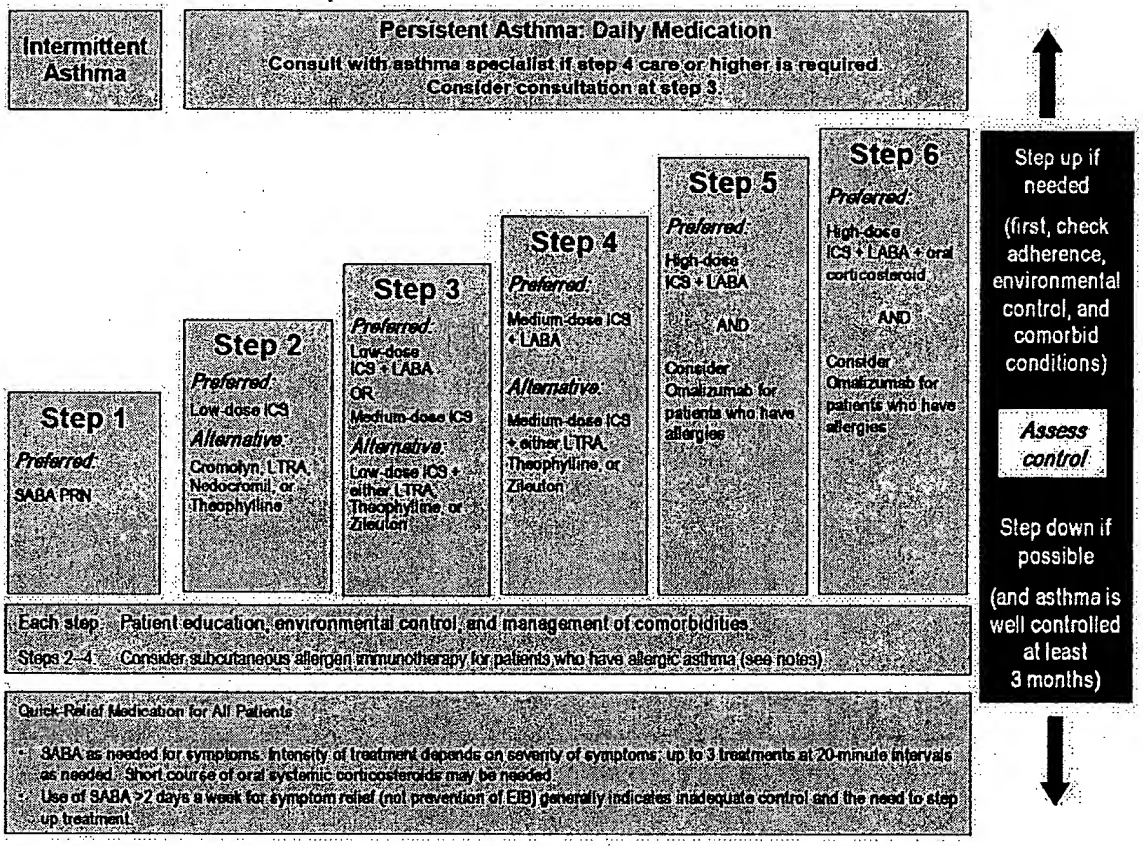
- **Anti-inflammatory Drugs.** Inhaled corticosteroids (ICS) are the key drugs used for controlling the underlying inflammation in asthma. Oral corticosteroids (OCS) when used for maintenance are reserved for patients with severe asthma. These drugs typically serve as maintenance medications.

- **Bronchodilators.** These drugs act principally to dilate the airways by relaxing airway smooth muscle. Bronchodilators reverse and/or inhibit airway constriction and related symptoms of acute asthma, but do not reverse airway inflammation. Bronchodilators come in two basic forms: maintenance medications such as long-acting beta agonists (LABA), which serve to produce prolonged bronchodilation up to 12 hours; and short-acting rescue medications, which are fast-acting and can alleviate the symptoms of asthma attacks for up to 4-6 hours.

- **Other medications** that may be considered when long-term control is still unattainable include methylxanthines, anticholinergics, leukotriene inhibitors, and IgE inhibitors (Xolair®).

As asthma symptoms increase, the dosage level and number of maintenance medications prescribed may be increased to reach an acceptable level of control. The drugs described above are generally introduced in a step-wise fashion as shown in Figure 2. Patients with severe asthma usually have more symptoms and therefore take higher doses and more types of medications than do patients with mild or moderate asthma.

Figure 2: Stepwise Approach for Managing Asthma in Adults
(Excerpted from NAEPP Guidelines 2007)




Despite the abundance of medications to treat asthma, there are significant limitations and risks associated with the existing standard of care, including:

- **Limited Efficacy in Patients with Severe Asthma.** A number of recent surveys indicate that symptoms are still poorly controlled in severe asthma patients, and that this patient population often continues to experience frequent and serious symptoms despite taking the highest prescribed doses of asthma medications (Partridge 2007). This limited efficacy is still only possible when the patient routinely takes their medicine as prescribed, typically twice a day, every day.

- **Poor Patient Compliance.** According to a 2007 report issued by the Global Initiative for Asthma (GINA 2007), non-compliance in taking asthma maintenance medications is estimated at approximately 50%. Non-compliance, in particular by severe asthmatics, may be an additional contributing factor to the increased number of emergency room visits and hospitalizations for these patients.

- **Side Effects.** Existing asthma medications carry with them possible and sometimes serious side effects. As with any medication, side effects typically become a greater concern as dosages increase and duration of treatment is extended indefinitely, which is the case for patients with severe asthma.

Steroids: Side effects of systemic corticosteroids (prednisone and other oral corticosteroids) range from mild annoyances to serious, irreversible damage, and they occur more frequently with higher doses and more prolonged treatment. Side effects associated with chronic administration of oral corticosteroids include compromised immune system; adrenal and growth suppression; osteoporosis; skin thinning; hypertension; cataracts; glaucoma; muscle weakness; and increased risk of infection. Short term side effects include stomach upset, headache, dizziness, trouble sleeping, fluid retention, weight gain, high blood pressure, loss of potassium, elevation of cholesterol levels and vision changes.

Bronchodilators: The side effects of short-acting rescue medications include rapid heartbeat, skeletal muscle tremor, potassium deficiency, increased lactic acid, headache and hyperglycemia. Long-acting beta-agonists may paradoxically cause severe exacerbations in some patients, and death when those episodes occur (GINA 2007).

Other Drugs: The side effects of Xolair (prescribed for allergic asthma) include anaphylaxis, injection site reactions and viral infections. Because of the potential for anaphylaxis, injections are administered (generally twice a month or once monthly) in the doctor's office, followed by a period of up to 1 hour of monitoring.

Monitoring serum concentrations of methylxanthine is essential to ensure that toxic concentrations are avoided. Symptoms of methylxanthine toxicity include severe headache, tachycardia, nausea, vomiting, heartburn, diarrhea, irritability, and restlessness.

- **Significant Ongoing Healthcare Burden.** Because the existing medical options provide poor control for some severe asthma patients, these patients are often forced to miss work or school and require unscheduled physician office visits, emergency room visits and hospitalizations. Thus patients with severe asthma create a significantly higher healthcare burden than the average asthma patient (Cisternas et al, 2003; Dolan et al, 2004).

As a result of limitations of existing medications, there remains a significant unmet medical need to improve the care for patients with severe asthma by better controlling their asthma symptoms. The asthma in this patient population with severe asthma is currently not well controlled by existing continual maintenance medical therapies. **Bronchial thermoplasty with the Alair System is a new long-lasting treatment option for this well defined population of patients with severe persistent asthma.**

## 4.0 Device Description

### 4.1 The Alair System

The Alair System comprises an Alair Catheter, an Alair Radiofrequency (RF) Controller, and accessories (Schematic in Figure 3, and photograph in Figure 4).

Figure 3: Schematic of The Alair System

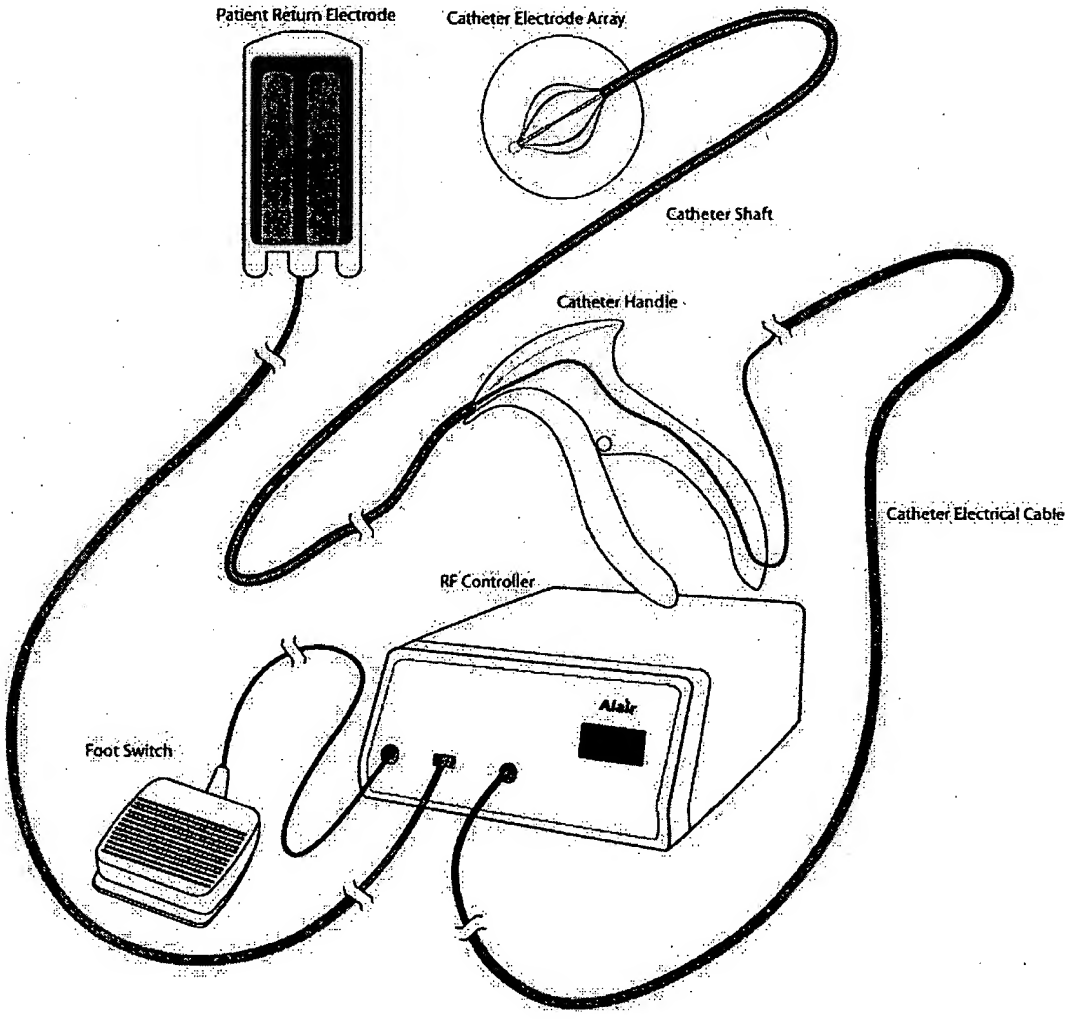
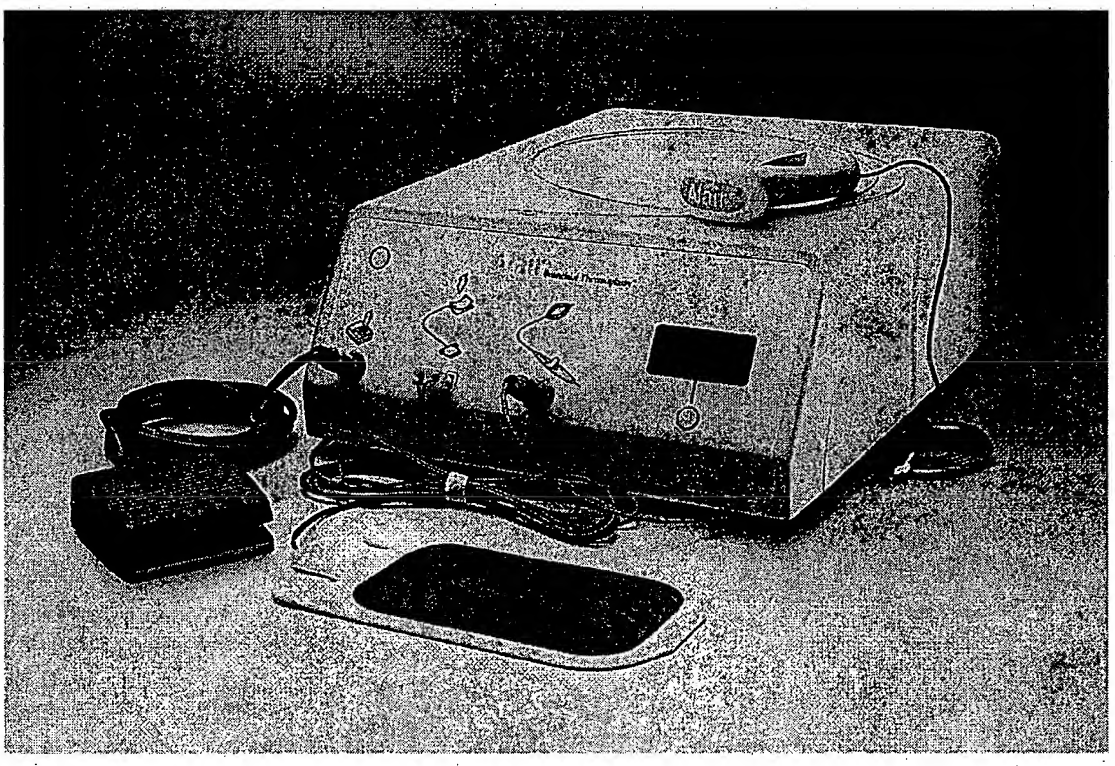


Figure 4: Photograph of The Alair System



4.1.1 Alair Catheter

The Alair Catheter (Figure 3) is a sterile, single-use, disposable device. The purpose of the Catheter is to deliver therapeutic RF energy to the airways.

The Alair Catheter is made up of:

1) an electrical cable that connects to the Alair RF Controller
2) a handle that is used to control the deployment of the electrode basket
3) the catheter shaft which is inserted through the working channel of a bronchoscope, and
4) an electrode basket at the distal tip of the catheter

The electrode basket has four stainless steel wire legs. Each leg is insulated with polyester heat shrink, leaving a 5 mm long exposed area at the center of the leg that is the active electrode, or energy delivering region. Visual contrast between the insulation and the exposed active electrode provides visual feedback to the user during bronchoscopy.

4.1.2 Alair RF Controller

The Alair RF Controller (Figure 3) provides temperature-controlled delivery of RF energy to the Catheter. RF technology has a long history of safe use for medical purposes.

The Alair RF Controller:

1) is reusable and provided non-sterile
2) delivers low-power (18 watts maximum), temperature-controlled RF energy to the airway at a treatment setting of 65°C for duration of 10 seconds
3) automatically limits the energy delivered in any activation to a maximum of 120 joules
4) includes safety algorithms that automatically shut off the RF Controller output in the event that atypical energy delivery is detected
5) incorporates hardware and software that limit current, voltage, power and temperature at any time during an activation, as well as the total energy administered during each activation

Numerous features have been incorporated into the design of the RF Controller and Alair Catheter to minimize the chance of unintended over-treatment. These features have been developed and tested through extensive pre-clinical studies.

### 4.1.3 Accessories

The Alair System has two accessories: a footswitch and patient return electrode (Figure 3). The footswitch assembly, which is provided with the RF Controller, comprises a commercially available footswitch, cable, and connector. It connects to the RF Controller front panel and is used to initiate the RF energy delivery. The patient return electrode is a standard, commercially available patient return electrode, which is used to complete the current path to the RF Controller.

## 5.0 Overview of the Bronchial Thermoplasty Procedure with the Alair System

### 5.1 Bronchial Thermoplasty for the Treatment of Severe Asthma

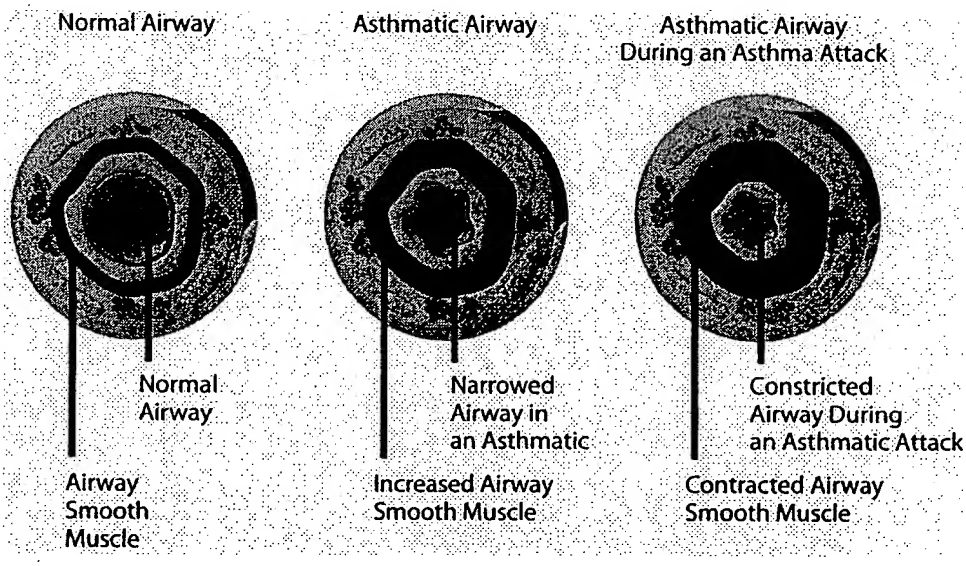
The development of bronchial thermoplasty for the treatment of severe asthma is based on the knowledge that the airway smooth muscle (ASM) plays a key role, negative in nature, in the manifestation of many of the symptoms of asthma.

### 5.2 Role of Airway Smooth Muscle

Airway smooth muscle is located within the walls of airways in the lung. An increase in the amount of airway smooth muscle in the lungs of patients with asthma has been demonstrated (An, 2007). This increased airway smooth muscle mass has the potential to increase airway responsiveness and bronchoconstriction in response to external stimuli, such as dust, allergens, cold air or stress, and cause asthma symptoms (An 2007). The excessive and inappropriate constriction of airway smooth muscle is recognized as a predominant feature of asthma, and therefore makes the airway smooth muscle a key target for pharmacotherapy.

Although current therapeutic regimens have been reasonably successful in controlling inflammation and contraction of airway smooth muscle in the majority of patients with asthma, a small proportion of patients with severe persistent asthma continue to suffer from excessive bronchoconstriction which is an integral part of an asthma "attack" (exacerbation). Therefore, it was theorized that a reduction of ASM would reduce the ability of the airways to narrow in response to a trigger, thereby providing a therapeutic benefit for patients with severe asthma (Figure 5).

Figure 5: Airway Smooth Muscle in Normal and Asthmatic Airways




Bronchial thermoplasty, a bronchoscopic procedure performed using the Alair System that delivers controlled radiofrequency energy to the airway walls, was proposed as a method of reducing the amount of airway smooth muscle. In considering this approach it is important to note that there is no known disease entity or physiological deficit

associated with loss of airway smooth muscle (Seow et al, 2001). Beyond the negative role of airway smooth muscle in causing bronchoconstriction in asthma, there remains an absence of scientific evidence to support a significant positive functional role for its presence in the lung (Cox et al, 2004). A number of potential functions of airway smooth muscle have been discussed, with the conclusion that none of these potential functions are essential to normal lung physiology (Mitzner et al, 2004). Nevertheless, it is important to note that bronchial thermoplasty with the Alair System is designed to reduce, but not altogether eliminate airway smooth muscle. The benefits of this ASM reduction have been confirmed in both preclinical testing and clinical studies of the Alair System.

### 5.3 Description of the Bronchial Thermoplasty Procedure

The bronchial thermoplasty procedure with the Alair System involves the delivery of controlled RF energy to the airway walls as a method for reducing the amount of ASM. The Alair System is designed for treatment of the airways distal to the mainstem bronchi down to airways of ≥ 3 mm in diameter. These airways normally represent about 80% of the total airway resistance in humans (West JB, ed., Respiratory Physiology, 2000).

Bronchial thermoplasty with the Alair System is a bronchoscopic procedure performed in a bronchoscopy suite as an outpatient procedure. To perform bronchial thermoplasty, standard moderate sedation and monitoring procedures as used for therapeutic bronchoscopies are utilized, following institutional guidelines. The procedure is performed as follows:

- The patient is appropriately prepped and placed under moderate sedation (formerly referred to as "conscious sedation"; standard sedation and monitoring protocols as for therapeutic bronchoscopy);
- A standard commercially available flexible bronchoscope is introduced into the bronchial tree (nasal or oral route), and the Alair Catheter is introduced into the airways through the working channel of the bronchoscope.
- The bronchoscope is then navigated to the first target treatment site, typically the most distal airway in the targeted lobe.
- Once the Catheter is positioned at the desired location in the airway, the electrode array at the tip of the Catheter is expanded to contact the airway wall, and the bronchoscopist activates the RF Controller to deliver RF energy to the tissue.
- The RF Controller delivers low-power, temperature-controlled RF energy to the airway, and terminates the energy delivery upon completion.
- Energy delivery during activation of the Catheter is controlled to a temperature of 65°C (149°F), a mild temperature sufficient to coagulate tissue without the charring or vaporization commonly seen in electrocautery. As a reference, the therapy temperature is 25°C (77°F) lower than that of a hot cup of coffee, which is about 90°C (194°F).

- The temperature set point, power limit, and delivery time are configured in the RF Controller software, and are not user adjustable.

- A single activation of the Catheter delivers RF energy over a distance of 5 mm (the length of the exposed electrodes within the electrode array). Audible and visual cues from the RF Controller signify proper delivery of RF energy. The complete treatment of a given airway requires delivery of RF energy along the entire accessible length of the airway via multiple adjacent activations.

- After each activation the Catheter is repositioned and subsequent activations are performed contiguously. This technique is used in all accessible airways distal to the mainstem bronchi and ≥ 3 mm in diameter. The Catheter is deployed from the distal to the proximal end of the airway being treated. This process is repeated in all airways that are accessible and planned for that bronchoscopy session.

- Following the procedure, the patient is monitored as in other routine bronchoscopy procedures. The patient is discharged to home following return of lung function ($FEV_1$) to a clinically acceptable level.

Bronchial thermoplasty is currently staged in 3 treatment sessions with a different region of the lung being treated during each session (one lower lobe in session 1; the second lower lobe in session 2; and both upper lobes in session 3). Treatment sessions are routinely scheduled at least 3 weeks apart.

### 5.4 Safety of Bronchoscopy in Patients with Asthma

Bronchial thermoplasty with the Alair System is performed bronchoscopically. The number and complexity of diagnostic and therapeutic procedures that can be performed bronchoscopically are increasing. Currently, over 500,000 therapeutic and diagnostic bronchoscopies are done each year in the United States. Bronchoscopy is a standard component of pulmonology training programs, with guidelines established by the American College of Chest Physicians: Guidelines on Interventional Pulmonary Procedures (Ernst 2003).

Bronchoscopy (both single and repeated) is a well-established procedure in the pulmonary community, and is routinely performed on patients with asthma. Examples of bronchoscopy procedures routinely performed are removal of mucus plugs, bronchoalveolar lavage (BAL) to collect cells and other substances of research interest from the lavage fluid obtained, segmental allergen challenge to understand the pathogenesis of allergen-driven airway inflammation, bronchial biopsy to study the morphology of asthmatic airways, and bronchial brushing to collect cells for *in vitro* study and histology. The use of bronchoscopy procedures in asthma patients is well established.

Potential bronchoscopy-related adverse events are well understood and manageable (Jarjour et al, 1998, Moore et al, 2005). Typical adverse events associated with bronchoscopy in patients with asthma (Elston et al, 2004) include:

- Bronchospasm (during & post-bronchoscopy)
- Worsening Asthma
- Shortness of breath
- Fever/influenza-like illness
- Pleuritic or non-specific chest pain
- Bleeding (blood-tinged sputum)
- Atelectasis

A review of more than 200 published articles by a National Institutes of Health panel in 1991 concluded that, extensive scientific data have accumulated that document that diagnostic bronchoscopy procedures can be performed safely to study the tracheobronchial tree of subjects with asthma and individuals with other obstructive pulmonary diseases (Bleecker et al, 1991).

### 5.5 Safety of Radiofrequency Energy in Medical Applications

Since its initial use in the operating room in 1926, radiofrequency (RF) energy has been widely used in medical and cosmetic applications. Its use through various medical devices and procedures has demonstrated its consistency, efficacy and safety. Applications of RF energy are used to heat, coagulate, and ablate tissue by controlling RF current density through optimization of output power and electrode size. Some current, safe medical applications of RF energy using devices cleared/approved by the US Food and Drug Administration include:

- Enlarged Prostate – to precisely reduce bulked tissue
- Liver Cancer – to reduce cancers
- Obstructive Sleep Apnea - to reduce the volume of the tongue
- Snoring – to reduce volume of soft tissue in and beneath of the palate
- Atrial Fibrillation – to modify conduction pathways
- Vision Correction - to reshape the cornea and correct vision
- Tightening Loose Joints – shrinking collagen to create a tighter joint
- Cosmetic Surgery – to tighten and conform skin

The output power delivered by the Alair System is on the lower end of the spectrum for currently used medical devices/systems.

## 6.0 Preclinical Evaluations of the Alair System

The preclinical proof of principle for the Alair System was established in 4 animal studies, including a randomized, sham-controlled study that followed dogs to 2 years post-treatment. A total of 35 dogs have undergone treatment with the Alair System, with long-term follow-up out to a maximum of 3 years.

A summary of these preclinical animal studies is provided in Table 1. Studies are listed from the most recent to the earliest.

Table 1: Preclinical Animal Studies with the Alair System

| Study | Longest Follow Up | Description of Study |
|---|---|---|
| QT-00334<br>30 dogs | 2 Years | **Randomized, blinded, sham-controlled study with 2 year follow-up designed in collaboration with FDA.**<br>Evaluated the long-term safety of the Alair System in 15 Alair treated dogs at 65°C compared to 15 sham control dogs. |
| QT-00090<br>6 dogs | 2.5 Years | Evaluated the safety of the Alair System in 6 dogs at 65°C (ancillary study) |
| QT-00075<br>12 dogs | 3 Years | Dose ranging study which evaluated the safety and effectiveness of the Alair System in 12 dogs at 55°C, 65°C, and 75°C.<br>(same test conditions as QT-00045) |
| QT-00045<br>2 dogs | 1 Year | Dose ranging study which evaluated the safety and effectiveness of the Alair System in 2 dogs at 55°C, 65°C, and 75°C.<br>(same test conditions as QT-00075) |

Collectively, the results from these studies provided the data needed to establish the treatment parameters and demonstrated that the procedure is well tolerated, and that the reduction in the airway smooth muscle is maintained to 3 years.

### 6.1 Treatment Parameters

The treatment parameters established as a result of these pre-clinical studies are:

- Treatment temperature = 65°C
- Treatment durations = 10 seconds
- Maximum power = 18 Watts

These treatment parameters were used in all human clinical studies.

# Appendix J

**FDA Due Diligence Log for Patent Extension**
**24 September 2004 to Present**

| Date | Item | Notes |
|---|---|---|
| 24 September 2004 | Conversation with N. Ogden of FDA | Discussion about bronchial thermoplasty workshop |
| 27 September 2004 | Letter to N. Ogden of FDA | Proposal for bronchial thermoplasty workshop. Also sent via e-mail. |
| 28 September 2004 | E-mail from C. Witten of FDA | Suggestion that bronchial thermoplasty workshop be part of public workshop |
| 28 September 2004 | E-mail to C. Witten of FDA | Request to keep bronchial thermoplasty workshop confidential |
| 28 September 2004 | E-mail from M. Provost of FDA | Request that workshop take one hour instead of two |
| 29 September 2004 | E-mail to M. Provost of FDA | Agreement to restrict workshop to one hour, discussion of topics |
| 8 November 2004 | Preparatory material for 19 November 2004 workshop | Sent to S. Brown of FDA |
| 19 November 2004 | Bronchial thermoplasty workshop at FDA | |
| 30 November 2004 | E-mail to S. Brown of FDA | Proposal to send list of questions with background information |
| 1 December 2004 | E-mail from S. Brown of FDA | Recommendation to send list of questions with protocol |
| 7 December 2004 | Request for Pre-IDE meeting | |
| 20 December 2004 | Discussion with S. Brown of FDA | Assignment of Pre-IDE number I040548. Discussion of scheduling |
| 4 January 2005 | Pre-IDE I040548 | Original submission |
| 6 January 2005 | E-mail from H. Lerner of FDA | Receipt of Pre-IDE I040548. |
| 6 January 2005 | E-mail to H. Lerner of FDA | "Guided tour" of Pre-IDE I040548 |

| Date | Item | Notes |
|---|---|---|
| 26 January 2005 | Letter to C. Witten of FDA | Additional information for Pre-IDE I040548. Also sent via e-mail. |
| 1 February 2005 | E-mail to S. Brown of FDA | Question regarding inclusion of Pre-IDE material in IDE submission |
| 2 February 2005 | E-mail from S. Brown of FDA | Response that it is acceptable to reference Pre-IDE in IDE |
| 6 February 2005 | E-mail to N. Ogden of FDA | Request to get FDA questions and comments prior to medical advisors meeting February 8 |
| 6 February 2005 | Letter to N. Ogden of FDA | Pre-IDE meeting participant list |
| 7 February 2005 | E-mail from C. Herzog of FDA | FDA comments on Pre-IDE |
| 14 February 2005 | Pre-IDE meeting | |
| 18 February 2005 | E-mail to C. Herzog of FDA | Question regarding number of IDE copies and drugs with AQLQ or symptom-free day claims |
| 18 February 2005 | E-mail from C. Herzog of FDA | Response regarding drug with AQLQ mentioned in labeling |
| 25 February 2005 | E-mail to S. Brown of FDA | Question regarding number of IDE copies |
| 25 February 2005 | E-mail from S. Brown of FDA | Response regarding number of IDE copies |
| 19 April 2005 | E-mail to N. Ogden of FDA | Provision of CVs for statisticians |
| 22 April 2005 | IDE application | Original submission |
| 27 April 2005 | E-mail to N. Ogden of FDA | Notification that IDE application had been sent |
| 28 April 2005 | IDE application receipt letter from FDA | Assigned IDE number G050082, dated 22 April 2005 and received 28 April 2005. |
| 6 May 2005 | IDE G050082/A001 | CONCEPT Trial publication and letters from Drs. Fitzgerald and Boulet |

| Date | Item | Notes |
|---|---|---|
| 9 May 2005 | E-mail from N. Ogden of FDA | Confirmation of receipt of A001 |
| May 2005 | E-mail to N. Ogden of FDA | Request for feedback May 27 |
| 26 May 2005 | E-mail to H. Lerner of FDA | Discussion of RISA study safety profile |
| 27 May 2005 | IDE G050082 disapproval letter from FDA | |
| 2 June 2005 | E-mail to H. Lerner of FDA | Draft letter responding to IDE disapproval letter |
| 10 June 2005 | E-mail to M. Janda of FDA | Request to postpone review team meeting until full response to IDE disapproval letter has been sent |
| 20 June 2005 | IDE G050082/A002 | Response to IDE disapproval letter |
| 18 July 2005 | Conversation with D.B. Tillman of FDA | Face-to-face discussion between G. French and D.B. Tillman in San Diego about development and FDA review history |
| 21 July 2005 | IDE G050082 conditional approval letter | |
| 2 August 2005 | E-mail to N. Ogden of FDA | Discussion of teleconference agenda for conditional approval response |
| 4 August 2005 | Teleconference with FDA | Discussed changes to the AIR2 Trial |
| 5 August 2005 | IDE G050082/S001 | Response to conditional approval letter |
| 10 August 2005 | E-mail from M. Janda of FDA | Confirmation of receipt of IDE G050082/S001 |
| 8 September 2005 | IDE G050082/S001 conditional approval letter | |
| 12 September 2005 | E-mail to N. Ogden and M. Janda of FDA | Request for extension for response to conditional approval letter |
| 2 November 2005 | IDE G050082/S002 | Part 11 compliance letter for Asthmatx and users of EDC/ePro systems |

| Date | Item | Notes |
|---|---|---|
| 7 November 2005 | IDE G050082/S003 | Response to conditional approval letter |
| 10 November 2005 | E-mail to M. Janda of FDA | Detail of changes from Rev. 2 to Rev. 3 of AIR2 Trial protocol |
| 14 November 2005 | IDE G050082/S004 | 5-Day Notice of Change to IDE G050082 |
| 20 November 2005 | E-mail to N. Ogden of FDA | Request to remove initial cap on number of U.S. institutions |
| 21 November 2005 | E-mail from N. Ogden of FDA | Response regarding institution cap, requesting it be proposed in supplement |
| 28 November 2005 | IDE G050082/S005 | Request to lift initial cap on number of U.S. institutions from 10 to 20 |
| 29 November 2005 | E-mail to M. Janda of FDA | Summary of submitted IDE supplements and requests for Doc Center check-in dates |
| 29 November 2005 | IDE G050082/S003 approval letter | |
| 30 November 2005 | E-mail from M. Janda of FDA | Response with due dates of IDE supplement reviews |
| 5 December 2005 | IDE G050082/S005 approval letter | Approval to lift initial cap on number of U.S.S institutions to 20 |
| 8 December 2005 | E-mail to M. Janda of FDA | Provision of RF Controller safety features and design verification testing tables from 5-Day Notice |
| 13 December 2005 | Conversation with M. Janda of FDA | Verbal approval of IDE G050082/S004 |
| 19 December 2005 | IDE G050082/S006 | Phase I report |
| 21 December 2005 | IDE G050082/S007 | Minor changes to AIR2 Trial protocol |
| 10 January 2006 | Conversation with M. Janda of FDA | Verbal approval of IDE G050082/S007 |
| 16 January 2006 | IDE G050082/S008 | Current investigator list |

| Date | Item | Notes |
|---|---|---|
| 10 February 2006 | IDE G050082/S009 | Additional clinical analysis to support expansion of AIR2 Trial |
| 2 March 2006 | Export permit request | For export to Brazil under IDE G050082 |
| 15 March 2006 | IDE G050082/S009 approval letter | |
| 22 March 2006 | IDE G050082/S010 | Request for increase in number of US subjects and number of treating US centers |
| 27 March 2006 | Export permit approval | |
| 28 March 2006 | E-mail to M. Janda of FDA | Request for IDE G050082/S010 review due date |
| 29 March 2006 | E-mail from M. Janda of FDA | Response with 22 April 2006 due date for S010 |
| 21 April 2006 | IDE G050082/S010 conditional approval | On condition of providing interim analysis reports |
| 5 June 2006 | IDE G050082/S011 | Agreement to submit interim reports |
| 6 June 2006 | IDE G050082/S012 | Minor changes to AIR2 Trial protocol |
| 28 June 2006 | Conversation with M. Janda of FDA | Verbal approval of IDE G050082/S012 |
| 3 July 2006 | IDE G050082/S011 conditional approval | |
| 19 July 2006 | IDE G050082/S013 | AIR2 Trial progress report |
| 3 August 2006 | IDE G050082/S014 | Agreement to submit interim reports on FDA-requested schedule |
| 14 August 2006 | Conversation with M. Janda of FDA | Notification that S014 was adequate and expansion of patients and centers was approved |
| 15 December 2006 | IDE G050082/S015 | Minor changes to AIR2 Trial protocol |

| Date | Item | Notes |
|---|---|---|
| 9 January 2007 | E-mail to M. Janda of FDA | Response to FDA request for additional information regarding S015 |
| 12 January 2007 | E-mail from M. Janda of FDA | Approval of IDE G050082/S015 |
| 17 January 2007 | IDE G050082/S016 | Current investigator list |
| 29 January 2007 | Conversation with M. Janda of FDA | Approval of IDE G05082/S016 |
| 30 January 2007 | E-mail to M. Janda of FDA | Notification of intent to file a Modular PMA |
| 30 January 2007 | E-mail from M. Janda of FDA | Agreement that Modular PMA process would be ideal |
| 15 February 2007 | E-mail to M. Janda of FDA | Request for discussion of Continued Access protocol |
| 27 February 2007 | Conversation with M. Janda of FDA | Discussion of Continued Access protocol |
| 20 March 2007 | IDE G050082/S017 | Request for Continued Access Trial |
| 21 March 2007 | E-mail to N. Ogden of FDA | Notification of impending arrival of S017 |
| 22 March 2007 | IDE G050082/S018 | 5-Day Notice of Change to AIR2 Trial |
| 20 April 2007 | IDE G05082/S017 conditional approval letter | |
| 21 April 2007 | Conversation with M. Janda of FDA | Verbal approval of IDE G050082/S018 |
| 1 June 2007 | IDE G050082/S019 | Request for extension to respond to S017 conditional approval letter |
| 7 June 2007 | Conversation with M. Janda of FDA | Verbal approval of S019 (request for extension) |
| 18 July 2007 | IDE G050082/S020 | Response to S017 conditional approval letter |
| 24 July 2007 | E-mail to M. Janda of FDA | Notification that annual progress report will be delayed |

| Date | Item | Notes |
|---|---|---|
| 27 July 2007 | E-mail from M. Janda of FDA | Response that annual progress report delay is acceptable |
| 31 July 2007 | PMA Module 1 | Original submission |
| 2 August 2007 | E-mail to M. Janda of FDA | Request on status of feedback from Dr. Shure regarding AIR3 Continued Access study |
| 2 August 2007 | E-mail from M. Janda of FDA | Response that Dr. Shure was not prepared to provide any advanced comments |
| 2 August 2007 | IDE G050082/S021 | Annual Progress Report. |
| 2 August 2007 | Module 1 receipt letter from FDA | Assigned PMA Module Number M070003/M001, dated 31 July 2007 and received 2 August 2007. |
| 6 August 2007 | E-mail to M. Janda of FDA | Notification that Module 1 had been sent to and received by FDA Document Mail Center, and that the design presented in Module 1 includes minor changes incorporated since the conduct of AIR2 under IDE 050082. |
| 7 August 2007 | E-mail to M. Janda of FDA | Notification that G050082/S021 had been sent to and received by FDA Document Mail Center. |
| 16 August 2007 | IDE G050082/S020 conditional approval letter | |
| 20 August 2007 | E-mail from M. Janda of FDA | Notification that IDE G050082/S020 was conditionally approved 16 August 2007 |
| 21 August 2007 | Conversation with M. Janda of FDA | Discussed Module 1, which he hadn't looked at yet, and AIR3 Continued Access Study, especially regarding enrollment cap and efficacy data collection. |
| 28 August 2007 | IDE G050082/S022 | Response to G050082/S020 conditional approval letter |

| Date | Item | Notes |
|---|---|---|
| 25 September 2007 | Conversation with M. Janda of FDA | Discussed Module 1, including software level of concern, and timing and content of Modules 2 and 3. |
| 28 September 2007 | IDE G050082/S022 approval letter | Approval for AIR3 Continued Access Registry. |
| 2 October 2007 | PMA Module 2 | Original submission |
| 3 October 2007 | Module 2 receipt letter from FDA | Assigned PMA Module Number M070003/M002, dated 2 October 2007 and received 3 October 2007. |
| 5 October 2007 | IDE G050082/S023 | 5-Day Notice of Change for ATS 2-5X3 (Gen B"). |
| 24 October 2007 | E-mail to M. Janda of FDA | Suggestion that software level of concern remain "Moderate" and provision of information on comparable devices classified as "Moderate." |
| 25 October 2007 | PMA Module 1 Amendment 1 | Provision of sterilization validation protocol, accelerated aging report, and information on heat shrink design change |
| 26 October 2007 | Module 1 Amendment 1 receipt letter from FDA | Assigned PMA Module Number M070003/M001/A001, dated 25 October 2007 and received 26 October 2007. |
| 7 November 2007 | Voice mail from M. Janda of FDA | Notification that FDA had converted IDE G050082/S023 from a 5-Day notice to a traditional 30-day supplement. |
| 8 November 2007 | Conversation with M. Janda of FDA | Notification that letter for Module 1 should be received in the next week, and that pulmonary device review was shifting to the Anesthesiology and Respiratory Devices branch in CDRH. |

| Date | Item | Notes |
|---|---|---|
| 8 November 2007 | IDE G050082/S023 disapproval letter from FDA | AIR3 Continued Access Registry protocol. |
| 11 November 2007 | E-mail to M. Janda of FDA | Request for time to talk about IDE feedback and inquiry on when Module 1 letter would be received. |
| 13 November 2007 | E-mail from M. Janda of FDA | Electronic copy of Module 1 letter. |
| 13 November 2007 | Module 1 deficiencies letter from FDA | |
| 19 November 2007 | Conversation with M. Janda of FDA | Discussion of some items from Module 1 deficiencies letter. |
| 5 December 2007 | IDE G050082/S024 | Response to S023 disapproval letter from FDA. |
| 6 December 2007 | IDE G050082/S024 receipt letter from FDA | |
| 18 December 2007 | E-mail to M. Janda of FDA | Provision of planned responses to Module 1 deficiencies letter. |
| 18 December 2007 | Voice mail from M. Janda of FDA | Request for more information regarding design change to coil described in IDE G050082/S024 |
| 20 December 2007 | IDE G050082/S025 | Second response to IDE G050082/S023 disapproval letter from FDA. |
| 21 December 2007 | IDE G050082/S025 receipt letter from FDA | |
| 4 January 2008 | IDE G050082/S024 disapproval letter from FDA | |
| 8 January 2008 | E-mail to M. Janda of FDA | Inquiry into review of manufacturing information by Office of Compliance. |
| 9 January 2008 | E-mail from M. Janda of FDA | Notification that Module 2 is considered closed. |
| 9 January 2008 | PMA Module 1 Amendment 2 | Response to Module 1 deficiencies letter. |

| Date | Item | Notes |
|---|---|---|
| 10 January 2008 | Module 1 Amendment 2 receipt letter from FDA | Assigned PMA Module Number M070003/M001/A002, dated 9 January 2008 and received 10 January 2008. |
| 10 January 2008 | Address change notification letter to FDA for PMA | |
| 10 January 2008 | Address change notification letter to FDA for IDE G050082 | |
| 11 January 2008 | Address change notification (PMA) receipt letter from FDA | Assigned PMA Shell Number M070003/A001, dated 10 January 2008 and received 11 January 2008. |
| 11 January 2008 | Module 2 closure letter from FDA | |
| 14 January 2008 | Address change notification (IDE) receipt letter from FDA | Assigned number G050082/S026. |
| 22 January 2008 | IDE G050082/S027 | AIR2 First Interim Analysis |
| 23 January 2008 | IDE G050082/S028 | AIR2 investigator list update |
| 24 January 2008 | IDE G050082/S027 receipt letter from FDA | |
| 24 January 2008 | IDE G050082/S028 receipt letter from FDA | |
| 4 February 2008 | Conversation with M. Janda of FDA | Discussion of PMA Module 1 Amendment 2 review timeline and responsibility, and IDE supplements S027 and S028. |
| 6 March 2008 | E-mail to M. Janda of FDA | Notification of plan to submit Module 3 in December 2008. |
| 7 March 2008 | Module 1 closure letter from FDA | |
| 13 March 2008 | PMA Shell Amendment letter to FDA | Formal notification of plan to submit Module 3 in December 2008. |

| Date | Item | Notes |
|---|---|---|
| 14 March 2008 | PMA Shell Amendment receipt letter from FDA | Assigned PMA Shell Number M070003/A002, dated 13 March 2008 and received 14 March 2008. |
| 20 March 2008 | E-mail to M. Husband of FDA | Comment on necessary pulmonologist expertise for advisory panel. |
| 24 March 2008 | E-mail from M. Husband of FDA | Acknowledgement from M. Husband. |
| 3 April 2008 | IDE G050082/S029 | Letter regarding AIR2 First Interim Analysis |
| 3 April 2008 | E-mail to M. Husband of FDA | Proposal of date and agenda for educational meeting |
| 8 April 2008 | E-mail from C. Kerns of FDA | Acknowledgement of 3 April e-mail to M. Husband, working on arranging meeting |
| 8 April 2008 | IDE G050082/S029 receipt letter from FDA | |
| 9 April 2008 | E-mail to M. Janda of FDA | Notification that sterilization validation report will be submitted in August 2008, last pending item for closure of AIR3 Continued Access Registry protocol under IDE. |
| 10 April 2008 | E-mail from M. Janda of FDA | Acknowledgement of 9 April 2008 e-mail. |
| 16 April 2008 | E-mail from C. Kerns of FDA | Proposal of new date for educational meeting |
| 16 April 2008 | E-mail to C. Kerns of FDA | Response to proposal of new date |
| 21 April 2008 | E-mail from C. Kerns of FDA | Response regarding scheduling for educational meeting |
| 21 April 2008 | E-mail to C. Kerns of FDA | Proposal of new date for educational meeting |
| 22 April 2008 | E-mail from C. Kerns of FDA | Acceptance of June 13 for education meeting |

| Date | Item | Notes |
|---|---|---|
| 9 May 2008 | IDE G050082/S030 | Letter regarding AIR2 Secondary Interim Analysis |
| 12 May 2008 | IDE G050082/S030 receipt letter from FDA | |
| 28 May 2008 | Conversation with C. Kerns of FDA | Status of IDE supplement regarding statistical question |
| 3 June 2008 | Educational meeting package sent to M. Husband | |
| 3 June 2008 | E-mail to C. Kerns of FDA | Inquiry into status of IDE supplement |
| 4 June 2008 | E-mail from C. Kerns of FDA | Response that supplement had been sent forward to management |
| 6 June 2008 | IDE G050082/S030 approval letter from FDA | |
| 13 June 2008 | Informational meeting with FDA | Introduction of the Alair System to Anesthesiology and Respiratory branch |
| 24 June 2008 | IDE G050082/S031 | Sterilization validation report |
| 17 July 2008 | IDE G050082/S031 approval from FDA | |
| 29 July 2008 | IDE G050082/S032 approval from FDA | |
| 29 July 2008 | IDE G050082/S033 approval from FDA | |
| 19 August 2008 | IDE G050082/S034 | Annual progress report |
| 20 August 2008 | IDE G050082/S034 receipt letter from FDA | |
| 16 September 2008 | Expedited review request | |
| 23 September 2008 | Conversation with C. Kerns of FDA | Confirmation that expedited review request was received |
| 23 September 2008 | E-mail to C. Kerns of FDA | Provision of expedited review guidelines |

| Date | Item | Notes |
|---|---|---|
| 30 September 2008 | E-mail to C. Kerns of FDA | Notification that Module 3 will be filed within 30 days to enable PMAI scheduling |
| 2 October 2008 | E-mail to C. Kerns of FDA | Proposal of dates for Pre-PMA meeting |
| 2 October 2008 | E-mail to C. Kerns of FDA | Proposal of revised dates for Pre-PMA meeting |
| 7 October 2008 | E-mail to C. Kerns of FDA | Checking on status of Pre-PMA meeting scheduling |
| 8 October 2008 | E-mail from C. Kerns of FDA | Arrangement of 5 November for Pre-PMA meeting |
| 8 October 2008 | E-mail to C. Kerns of FDA | Request for 2 hours for Pre-PMA meeting |
| 8 October 2008 | E-mail from C. Kerns of FDA | Agreement for 2 hours for Pre-PMA meeting |
| 8 October 2008 | E-mail to C. Kerns of FDA | Request for list of FDA's attendees for Pre-PMA meeting |
| 14 October 2008 | Conversation with C. Kerns of FDA | Update on expedited review process, meeting attendance, FDA personnel, stability protocol |
| 17 October 2008 | Approval letter for expedited review | |
| 28 October 2008 | E-mail to C. Kerns of FDA | Minutes from 13 June 2008 meeting |
| 3 November 2008 | Letter to C. Kerns of FDA | Attendees, biographies, and slides for Pre-PMA meeting |
| 26 November 2008 | E-mail from C. Kerns of FDA | Feedback from Pre-PMA meeting |
| 29 December 2008 | PMA Module 3 | Original submission |
| 30 December 2008 | Module 3 receipt letter from FDA | From ENT division |
| 31 December 2008 | Module 3 receipt letter from FDA | From Anesthesiology division |

| Date | Item | Notes |
|---|---|---|
| 5 January 2009 | Letter to C. Kerns of FDA | PMA review checklist (P080032/A001) |
| 6 January 2009 | Conversation with G. Michaud of FDA | Reviewer assignment (Michael Ryan) and request for FDA schedule and planning for Day-100 and panel meetings |
| 7 January 2009 | P080032/A001 receipt letter from FDA | From Anesthesiology division |
| 9 January 2009 | E-mail from M. Ryan of FDA | Introduction from new reviewer and notice of PMA number assignment (P080032) |
| 12 January 2009 | E-mail to G. Michaud of FDA | Request for dates and schedules |
| 15 January 2009 | E-mail from M. Ryan of FDA | Request for statistics information, location of records, and extra hard copy |
| 16 January 2009 | E-mail to M. Ryan of FDA | Response re: statistics files, location of records, and extra hard copy |
| 20 January 2009 | E-mail to M. Ryan of FDA | Notice of duplicate Module 3 receipt letters |
| 21 January 2009 | E-mail to M. Ryan of FDA | Question re: to which branch we should send IDE supplements |
| 21 January 2009 | E-mail from M. Ryan of FDA | Response that IDE supplements should be sent to Anesthesiology & Respiratory branch |
| 22 January 2009 | Conversation with L. Rodriguez of FDA | BIMO inspection scheduling for Santa Casa |
| 26 January 2009 | Letter to M. Ryan of FDA | AIR2 Trial Investigator/Site Data Set CDs |
| 28 January 2009 | E-mail from L. Rodriguez of FDA | BIMO inspection announcement for Santa Casa |
| 28 January 2009 | E-mail to L. Rodriguez of FDA | Response re: Santa Casa BIMO inspection scheduling |

| Date | Item | Notes |
|---|---|---|
| 29 January 2009 | E-mail from L. Rodriguez of FDA | Response re: Santa Casa BIMO inspection scheduling |
| 29 January 2009 | E-mail to L. Rodriguez of FDA | Response re: Santa Casa BIMO inspection scheduling |
| 30 January 2009 | E-mail to M. Ryan of FDA | Question re: 2/5 panel meeting |
| 30 January 2009 | E-mail from M. Ryan of FDA | Response re: 2/5 panel meeting |
| 3 February 2009 | P080032/A002 | ClinicalTrials.gov certification (Form FDA 3674) |
| 3 February 2009 | E-mail to L. Rodriguez of FDA | Hotel information for Santa Casa BIMO inspection |
| 3 February 2009 | Letter from O. Barry of FDA | BIMO inspection announcement for Laval |
| 4 February 2009 | P080032/A002 receipt letter | |
| 4 February 2009 | E-mail from L. Rodriguez of FDA | Response re: hotels for Santa Casa BIMO inspection |
| 4 February 2009 | E-mail to L. Rodriguez of FDA | Travel arrangements for Santa Casa BIMO inspection |
| 5 February 2009 | E-mail to M. Ryan of FDA | Inspection status update |
| 6 February 2009 | E-mail from O. Barry of FDA | BIMO inspection announcement for Laval |
| 9 February 2009 | E-mail from O. Barry of FDA | Question re: QSIT |
| 9 February 2009 | E-mail to O. Barry of FDA | Response re: QSIT |
| 10 February 2009 | E-mail to M. Ryan of FDA | Question re: PMA filing date and 90-day letter due date |
| 11 February 2009 | E-mail from M. Ryan of FDA | Response re: PMA filing date and poolability question |
| 11 February 2009 | E-mail to M. Ryan of FDA | Response re: poolability and phone call scheduling |
| 12 February 2009 | E-mail from M. Ryan of FDA | Confirmation of 2/18 call |
| 17 February 2009 | P080032 filing decision | Filing date: 30 December 2008<br>Expedited processing |

| Date | Item | Notes |
|---|---|---|
| 17 February 2009 | P080032/A003 receipt letter from FDA | |
| 18 February 2009 | Conversation with M. Ryan of FDA | 90-day letter timing, 100-day meeting, panel meeting, FDA management |
| 18 February 2009 | E-mail to M. Ryan of FDA | Confirmation of April 29 vs. April 30 panel meeting date |
| 19 February 2009 | E-mail to M. Ryan of FDA | Notification re: overdue filing decision letter |
| 19 February 2009 | E-mail from M. Ryan of FDA | Response re: overdue filing decision letter |
| 19 February 2009 | E-mail to M. Ryan of FDA | Poolability amendment |
| 19 February 2009 | Conversation with L. Brown of FDA | Logistics for BIMO inspection at Santa Casa |
| 20 February 2009 | E-mail to L. Brown of FDA | Santa Casa bimo inspection arrangements |
| 24 February 2009 | E-mail to M. Ryan of FDA | Question re: timing of Panel Pack |
| 25 February 2009 | E-mail from M. Ryan of FDA | Response re: timing of Panel Pack, update on QSIT inspection scheduling |
| 26 February 2009 | E-mail to M. Ryan of FDA | Question re: dates of panel meeting and 100-day meeting |
| 26 February 2009 | E-mail to N. Patel of FDA | Question re: date of panel meeting |
| 2 March 2009 | E-mail from M. Ryan of FDA | Response re: dates of panel meeting and 100-day meeting |
| 3 March 2009 | E-mail to M. Ryan of FDA | 4/29 panel meeting scheduling |
| 5 March 2009 | E-mail to M. Ryan of FDA | Update on BIMO inspection at Santa Casa, dates for 100-day meeting and panel meeting, request for interim feedback prior to 90-day letter |
| 6 March 2009 | E-mail from M. Ryan of FDA | Response re: dates for 100-day meeting and panel meeting |

| Date | Item | Notes |
|---|---|---|
| 18 March 2009 | E-mail to M. Ryan of FDA | Update on BIMO inspection at Laval, QSIT inspection at LSO, dates for 90-day letter, 100-day meeting, and panel meeting |
| 19 March 2009 | E-mail to M. Ryan of FDA | Number of Panel Pack copies |
| 20 March 2009 | E-mail from N. Patel of FDA | Postponement of panel meeting |
| 20 March 2009 | E-mail from M. Ryan of FDA | Update on impending letter identifying issues to address |
| 20 March 2009 | E-mail to M. Ryan of FDA | Expectation of 90-day letter on March 27th and contact information in D. Brown's absence |
| 27 March 2009 | E-mail to M. Ryan of FDA | Request re: status of 90-day letter |
| 30 March 2009 | E-mail to G. Michaud of FDA | Notice that 90-day letter has not arrived |
| 31 March 2009 | E-mail from S. Runner of FDA | Apology for letter delay and expectation that it should arrive in 1-2 days |
| 31 March 2009 | Conversation with S. Runner of FDA | Status of 90-day letter and panel meeting |
| 3 April 2009 | Major Deficiency Letter | |
| 9 April 2009 | E-mail from M. Ryan of FDA | Setting up a call to discuss questions and next steps |
| 9 April 2009 | E-mail to M. Ryan of FDA | Response regarding setting up a call |
| 10 April 2009 | E-mail from M. Ryan of FDA | Labeling questions |
| 10 April 2009 | E-mail to M. Ryan of FDA | Response regarding call and AQLQ question clarification |
| 13 April 2009 | E-mail to M. Ryan of FDA | Request for confirmation of 4/14 call and AQLQ question clarification |
| 13 April 2009 | E-mail from M. Ryan of FDA | Confirmation of 4/14 call |
| 14 April 2009 | Conversation with M. Ryan of FDA | Scheduling for sterility/packaging call, organization, review schedule |
| 22 April 2009 | E-mail to M. Ryan of FDA | Discussion topics for teleconference |

| Date | Item | Notes |
|---|---|---|
| 22 April 2009 | E-mail to M. Ryan of FDA | Request for call |
| 22 April 2009 | E-mail from M. Ryan of FDA | Proposal for call time |
| 22 April 2009 | E-mail to M. Ryan of FDA | Proposal for call time |
| 22 April 2009 | E-mail to M. Ryan of FDA | Topics for 4/22 call |
| 22 April 2009 | Conversation with M. Ryan of FDA | Scheduling for sterility/packaging call, statistics questions, organization, review schedule |
| 23 April 2009 | E-mail to M. Ryan of FDA | Follow-up on meeting with sterility/packaging engineer |
| 24 April 2009 | E-mail from M. Ryan of FDA | Response regarding availability of sterility/packaging engineer |
| 24 April 2009 | Letter from G. Keely of FDA | "No response required" for Santa Casa BIMO inspection |
| 28 April 2009 | E-mail from M. Ryan of FDA | Answers from statisticians regarding 4/22 questions |
| 28 April 2009 | E-mail from M. Ryan of FDA | Scheduling of sterility/packaging discussion |
| 30 April 2009 | E-mail from M. Ryan of FDA | Confirmation of sterility/packaging discussion |
| 30 April 2009 | E-mail to M. Ryan of FDA | Confirmation of sterility/packaging discussion |
| 30 April 2009 | E-mail from M. Ryan of FDA | Confirmation of receipt of packaging testing flowchart |
| 1 May 2009 | E-mail to M. Ryan of FDA | Cancellation of sterility/packaging discussion and request for QT-00501 clarification |
| 1 May 2009 | E-mail to M. Ryan of FDA | Follow-up on receipt of cancellation e-mail |
| 1 May 2009 | E-mail from M. Ryan of FDA | Confirmation of receipt of cancellation e-mail, request for submission timeframe |
| 6 May 2009 | E-mail to M. Ryan of FDA | Request for teleconference |
| 6 May 2009 | E-mail from M. Ryan of FDA | Proposal of 5/8 for teleconference |

| Date | Item | Notes |
|---|---|---|
| 6 May 2009 | E-mail to M. Ryan of FDA | Confirmation and details of 5/8 teleconference |
| 6 May 2009 | E-mail to M. Ryan of FDA | List of ATS posters and presentations |
| 8 May 2009 | Letter from G. Keely of FDA | "No response required" for Laval BIMO inspection |
| 8 May 2009 | E-mail to M. Ryan of FDA | Request for call with S. Turtil of FDA regarding sterility/packaging |
| 12 May 2009 | E-mail to M. Ryan of FDA | Follow-up on availability of S. Turtil for sterility/packaging discussion |
| 14 May 2009 | E-mail from M. Ryan of FDA | Scheduling for response and sterility/packing discussions |
| 14 May 2009 | E-mail to M. Ryan of FDA | Scheduling for response and sterility/packing discussions |
| 20 May 2009 | E-mail to M. Ryan of FDA | 6/1 availability for call |
| 20 May 2009 | E-mail from M. Ryan of FDA | Scheduling for response and sterility/packing discussions |
| 22 May 2009 | E-mail to M. Ryan of FDA | Available dates for response discussion |
| 22 May 2009 | E-mail from M. Ryan of FDA | Response with FDA's available dates for response discussion |
| 22 May 2009 | E-mail to M. Ryan of FDA | Response to FDA's available dates for response discussion |
| 26 May 2009 | E-mail to M. Ryan of FDA | Availability for 5/27 and 6/3 calls |
| 26 May 2009 | E-mail from M. Ryan of FDA | Response with FDA's available dates for response and sterility/packing discussion |
| 27 May 2009 | E-mail to M. Ryan of FDA | Don Berry availability for 6/3 call |
| 27 May 2009 | E-mail to M. Ryan of FDA | Draft responses for Questions 2-10 and proposed agenda for call |
| 27 May 2009 | Conversation with FDA | Discussion with S. Turtil regarding sterility and packaging deficiencies |

| Date | Item | Notes |
|---|---|---|
| 27 May 2009 | E-mail to M. Ryan of FDA | Thank-you note for arranging sterility/packaging call and promise to incorporate into response |
| 28 May 2009 | E-mail from M. Ryan of FDA | Setup of June 3rd call |
| 28 May 2009 | E-mail to M. Ryan of FDA | Draft response to Question #1 |
| 28 May 2009 | E-mail to M. Ryan of FDA | Thank-you response for setting up call |
| 2 June 2009 | E-mail from M. Ryan of FDA | Participants and agenda for 6/3 call |
| 2 June 2009 | E-mail to M. Ryan of FDA | Participants for 6/3 call |
| 3 June 2009 | Conversation with FDA | Discussion with D. Shure and statisticians regarding deficiencies |
| 5 June 2009 | Letter to S. Runner of FDA | Request for pulmonologists on panel |
| 9 June 2009 | P080032/A004 receipt letter from FDA | Amendment A004 is the Letter to S. Runner regarding pulmonologists on panel |
| 10 June 2009 | Response to Major Deficiency Letter | |
| 11 June 2009 | P080032/A005 receipt letter from FDA | Amendment A005 is the Response to Major Deficiency Letter |
| 11 June 2009 | E-mail to M. Ryan of FDA | Electronic copy of Major Deficiency Letter Response |
| 11 June 2009 | E-mail to M. Ryan of FDA | Check on receipt of electronic copy of response |
| 12 June 2009 | E-mail from M. Ryan of FDA | Confirmation of receipt of electronic copy of response |
| 16 June 2009 | E-mail to M. Ryan of FDA | Presenter availability for panel dates |
| 20 June 2009 | E-mail to M. Ryan of FDA | Request for call |
| 23 June 2009 | E-mail from M. Ryan of FDA | Response re: request for call |
| 24 June 2009 | Conversation with M. Ryan of FDA | Panel dates and constituency, panel pack, IFU, Dr. Slutsky |

| Date | Item | Notes |
|---|---|---|
| 24 June 2009 | Letter to M. Ryan of FDA | Letter with Calendar of Events leading up to panel meeting |
| 25 June 2009 | P080032/A006 receipt letter from FDA | Amendment A006 is the Calendar of Events letter |
| 2 July 2009 | E-mail to M. Ryan of FDA | Negotiation of panel dates |
| 2 July 2009 | E-mail from M. Ryan of FDA | Tentative panel date of 10/27 |
| 6 July 2009 | E-mail to N. Patel of FDA | Request for availability of pre-10/27 dates |
| 6 July 2009 | E-mail to M. Ryan of FDA | Request for September or early October panel date |
| 13 July 2009 | E-mail to M. Ryan of FDA | Negotiation of panel dates |
| 14 July 2009 | E-mail from M. Ryan of FDA | Request for call re: panel dates |
| 14 July 2009 | E-mail to M. Ryan of FDA | Proposal for 7/14 call |
| 14 July 2009 | E-mail from M. Ryan of FDA | Confirmation of 7/14 call |
| 14 July 2009 | E-mail to M. Ryan of FDA | Number to call |
| 14 July 2009 | E-mail to M. Ryan of FDA | Request for early discussion of sterility/packaging review |
| 15 July 2009 | E-mail from M. Ryan of FDA | Response regarding early discussion ("no") |
| 17 July 2009 | E-mail to M. Ryan of FDA | Request for status of Panel date |
| 17 July 2009 | E-mail from M. Ryan of FDA | Update on status of Panel date |
| 23 July 2009 | E-mail to M. Ryan of FDA | Request for status of Panel date |
| 23 July 2009 | E-mail to M. Ryan of FDA | Thanks for feedback |
| 24 July 2009 | E-mail from N. Patel of FDA | Update on status of Panel date (looking at 10/29) |
| 24 July 2009 | E-mail to N. Patel of FDA | Request for status of Panel date |
| 24 July 2009 | E-mail from N. Patel of FDA | Update on status of Panel date |
| 24 July 2009 | E-mail to N. Patel of FDA | Thanks for status update |
| 27 July 2009 | E-mail to N. Patel of FDA | Request for status of Panel date |

| Date | Item | Notes |
|---|---|---|
| 28 July 2009 | E-mail from N. Patel of FDA | Update on status of Panel date (10/29 not good) |
| 28 July 2009 | E-mail to N. Patel of FDA | Thanks of status update |
| 29 July 2009 | E-mail to N. Patel of FDA | Request for status of Panel date |
| 30 July 2009 | E-mail to N. Patel of FDA | Request for status of Panel date |
| 31 July 2009 | E-mail from N. Patel of FDA | Update on status of Panel date (11/6?) |
| 5 August 2009 | E-mail to N. Patel of FDA | Request for status of Panel date |
| 6 August 2009 | E-mail from N. Patel of FDA | Moving forward with 10/28 Panel date |
| 6 August 2009 | E-mail to N. Patel of FDA | Request for confirmation of 10/28 Panel date |
| 6 August 2009 | Email from N. Patel of FDA | Confirmation of 10/28 Panel date |
| 11 August 2009 | E-mail to N. Patel of FDA | Request for city/hotel of Panel meeting and public forum schedule |
| 12 August 2009 | E-mail from N. Patel of FDA | Confirmation of Gaithersburg as Panel city and 1-hour public forum |
| 13 August 2009 | E-mail to M. Ryan of FDA | Request to contact OSB |
| 14 August 2009 | E-mail to M. Ryan of FDA | Request for update on Major Deficiency Letter Response |
| 20 August 2009 | E-mail to M. Ryan of FDA | Request to contact OSB |
| 25 August 2009 | E-mail from M. Ryan of FDA | Request for update call |
| 25 August 2009 | E-mail to M. Ryan of FDA | Proposal for 8/26 call |
| 26 August 2009 | E-mail from M. Ryan of FDA | Confirmation of 8/26 call |
| 26 August 2009 | BIMO inspection results letter to Dr. Castro | |
| 3 September 2009 | Conversation with M. Ryan of FDA | Status of deficiency letter response review, plan to work with OSB |
| 10 September 2009 | E-mail to M. Ryan of FDA | Request to contact OSB |
| 11 September 2009 | E-mail from N. Patel of FDA | Panel Pack logistics |

| Date | Item | Notes |
|---|---|---|
| 11 September 2009 | E-mail from N. Patel of FDA | Request to ignore previous e-mail's subject line (Ethicon) |
| 11 September 2009 | E-mail to N. Patel of FDA | Panel details |
| 11 September 2009 | E-mail to N. Patel of FDA | Proposed Panel Pack calendar |
| 14 September 2009 | E-mail to N. Patel of FDA | Confirmation of sample Panel Pack submission date |
| 14 September 2009 | Conversation with N. Patel of FDA | Timing of Panel Pack submissions and panel membership |
| 15 September 2009 | E-mail to M. Ryan of FDA | Request for call |
| 15 September 2009 | E-mail from M. Ryan of FDA | Response to call request |
| 15 September 2009 | E-mail to M. Ryan of FDA | Number to call |
| 15 September 2009 | E-mail from M. Ryan of FDA | Deficiency list |
| 15 September 2009 | E-mail to M. Ryan of FDA | Working on availability for 9/17 call |
| 15 September 2009 | E-mail to N. Patel of FDA | Agreement on Panel calendar |
| 16 September 2009 | E-mail to M. Ryan of FDA | Request for short call |
| 16 September 2009 | E-mail to M. Ryan of FDA | Request for call-in information for 9/17 teleconference |
| 16 September 2009 | E-mail to M. Ryan of FDA | Request for clarification on FDA 9/15/09 E-mail Question #3 |
| 17 September 2009 | E-mail from M. Ryan of FDA | Call-in information for 9/17 teleconference |
| 17 September 2009 | E-mail to M. Ryan of FDA | Request for call before teleconference |
| 17 September 2009 | Conversation with OSB at FDA | Initial discussion with OSB regarding Post-Approval Study |
| 17 September 2009 | Conversation with M. Ryan of FDA | Clarification that FDA 9/15/09 E-mail Question #3 was specific to the device and not packaging |
| 17 September 2009 | E-mail to M. Ryan of FDA | List of participants on 9/17 OSB call |
| 17 September 2009 | E-mail from M. Ryan of FDA | Contact info for J. Chen of OSB |
| 18 September 2009 | E-mail to M. Ryan of FDA | Follow-up on call with OSB |

| Date | Item | Notes |
|---|---|---|
| 18 September 2009 | E-mail from J. Chen of OSB | No content (subject: PAS outline) |
| 21 September 2009 | E-mail to N. Patel of FDA | Questions re: Panel meeting |
| 21 September 2009 | E-mail from N. Patel of FDA | Notice that David Spindell is industry rep, panel makeup, AV |
| 22 September 2009 | E-mail from J. Chen of OSB | No content (subject: PAS outline) |
| 22 September 2009 | E-mail to J. Chen of OSB | Update on status of PAS outline |
| 23 September 2009 | E-mail to N. Patel of FDA | Thanks for feedback |
| 22 September 2009 | E-mail to N. Patel of FDA | Proposed agenda times |
| 23 September 2009 | E-mail from N. Patel of FDA | Acceptance of agenda times |
| 23 September 2009 | E-mail to N. Patel of FDA | E-copy of sample Panel Pack |
| 23 September 2009 | Minor revisions to AIR2 Clinical Study Report | Amendment to PMA correction hospitalization data |
| 24 September 2009 | E-mail from J. Chen of OSB | Request to have the PAS outline by end of day |
| 24 September 2009 | E-mail to M. Ryan of FDA | Response to FDA 9/15/09 E-mail Question #3 |
| 24 September 2009 | Conversation with M. Ryan of FDA | Request for additional information in Panel Pack |
| 24 September 2009 | E-mail from M. Ryan of FDA | Request for copy of Q0044 |
| 24 September 2009 | E-mail to M. Ryan of FDA | Copy of Q0044 Rev D |
| 24 September 2009 | E-mail to J. Chen of OSB | Response to FDA 9/15/09 E-mail Question #2 and PAS outline |
| 24 September 2009 | E-mail from J. Chen of OSB | Thank-you for PAS outline |
| 25 September 2009 | E-mail from J. Chen of OSB | Request for outline of AIR2 follow-up |
| 28 September 2009 | E-mail to M. Ryan of FDA | Request for teleconference |
| 28 September 2009 | Teleconference with M. Ryan of FDA | Panel-related topics |
| 28 September 2009 | E-mail to N. Patel of FDA | Request for industry rep phone number |

| Date | Item | Notes |
|---|---|---|
| 28 September 2009 | E-mail to M. Ryan of FDA | Question re: timing and delivery of FDA Questions and Panel Pack |
| 29 September 2009 | E-mail from N. Patel of FDA | Industry rep phone number |
| 29 September 2009 | E-mail to N. Patel of FD | Thanks for industry rep phone number |
| 29 September 2009 | E-mail from J. Chen of OSB | Request for outline of AIR2 follow-up |
| 29 September 2009 | E-mail to J. Chen of OSB | Update on outline and request for feedback |
| 29 September 2009 | E-mail from J. Chen of OSB | Request to clearly state the study endpoints |
| 29 September 2009 | E-mail to M. Ryan of FDA | Update on Panel Pack, unblinding, PAS |
| 30 September 2009 | E-mail from M. Ryan of FDA | Update on blinding analysis and Panel Pack |
| 30 September 2009 | E-mail to M. Ryan of FDA | Response to FDA 9/15/09 E-mail Question #1 |
| 30 September 2009 | E-mail to J. Chen of OSB | AIR2 follow-up outline |
| 1 October 2009 | E-mail to M. Ryan of FDA | Commitment to 10/1 AM delivery of hemoptysis response |
| 1 October 2009 | E-mail to M. Ryan of FDA | Request for feedback on response to FDA 9/15/09 E-mail Question #3 |
| 1 October 2009 | E-mail to M. Ryan of FDA | Response to FDA 9/15/09 E-mail Question #4 |
| 1 October 2009 | E-mail from M. Ryan of FDA | Follow-up question on Question #4 |
| 1 October 2009 | E-mail to M. Ryan of FDA | Response re: Question #4 follow-up |
| 1 October 2009 | E-mail to M. Ryan of FDA | Request for update on Question #3 |
| 1 October 2009 | E-mail to M. Ryan of FDA | Panel Pack |
| 2 October 2009 | E-mail to M. Ryan of FDA | IFU in Panel Pack |
| 2 October 2009 | E-mail to M. Ryan of FDA | Formal response re: Question #4 follow-up |

| Date | Item | Notes |
|---|---|---|
| 2 October 2009 | E-mail from M. Ryan of FDA | Feedback re: responses and electronic copy of Panel Pack |
| 2 October 2009 | E-mail to M. Ryan of FDA | Follow-up on receipt of blinding analysis |
| 2 October 2009 | E-mail from M. Ryan of FDA | Blinding analysis not received |
| 2 October 2009 | E-mail to M. Ryan of FDA | Clarification re: page numbers in electronic copy of Panel Pack |
| 2 October 2009 | E-mail from M. Ryan of FDA | Response re: page numbers in electronic copy of Panel Pack |
| 5 October 2009 | E-mail from D. Shure of FDA | Request for definition of "asthma (multiple symptom)" |
| 5 October 2009 | E-mail to D. Shure of FDA | Response with definition of "asthma (multiple symptom)" |
| 5 October 2009 | E-mail from N. Patel of FDA | Draft FDA Executive Summary |
| 5 October 2009 | E-mail to N. Patel of FDA | Timing of FDA Questions |
| 5 October 2009 | E-mail from N. Patel of FDA | Response that FDA Questions would not be sent before Panel Pack |
| 6 October 2009 | E-mail to N. Patel of FDA | Response that M. Ryan stated Questions and Executive Summary would come together |
| 6 October 2009 | E-mail from N. Patel of FDA | Request for status of Panel Pack, update on Questions |
| 6 October 2009 | E-mail to N. Patel of FDA | Response that other companies received FDA Questions before Panel Pack |
| 6 October 2009 | E-mail from N. Patel of FDA | Request for status of Panel Pack, update on FDA Questions |
| 6 October 2009 | E-mail to N. Patel of FDA | Panel Packs were shipped 10/5 |
| 6 October 2009 | E-mail from N. Patel of FDA | Response that he would confirm when Panel Packs are received |
| 6 October 2009 | E-mail to N. Patel of FDA | FedEx delivery of Panel Packs |

| Date | Item | Notes |
|---|---|---|
| 6 October 2009 | E-mail from N. Patel of FDA | Confirmation that Panel Packs were received |
| 6 October 2009 | E-mail to N. Patel of FDA | Request for update on FDA Questions |
| 6 October 2009 | E-mail from N. Patel of FDA | No new update on FDA Questions |
| 6 October 2009 | E-mail to N. Patel of FDA | Thanks for update |
| 6 October 2009 | P080032/A007 receipt letter | A007 is the blinding analysis CD |
| 7 October 2009 | E-mail from N. Patel of FDA | Draft FDA Questions |
| 7 October 2009 | E-mail to N. Patel of FDA | Request for call to discuss feedback with D. Shure |
| 7 October 2009 | E-mail from N. Patel of FDA | Response to request for call |
| 7 October 2009 | E-mail to N. Patel of FDA | Request for 48 hours to review FDA Questions |
| 7 October 2009 | E-mail to N. Patel of FDA | Comments on FDA Executive Summary |
| 7 October 2009 | E-mail to N. Patel of FDA | Copy of Executive Summary comments for Dr. Shure |
| 8 October 2009 | E-mail from N. Patel of FDA | Request that comments on FDA Questions be sent as soon as possible |
| 8 October 2009 | E-mail to N. Patel of FDA | Response that comments on FDA Questions would be sent shortly |
| 8 October 2009 | E-mail to N. Patel of FDA | Comments on FDA Questions |
| 8 October 2009 | E-mail to N. Patel of FDA | Check to see if comments on FDA Questions were received |
| 8 October 2009 | E-mail from N. Patel of FDA | Confirmation that comments were received |
| 8 October 2009 | E-mail to N. Patel of FDA | Cell phone number if needed |
| 8 October 2009 | E-mail from J. Chen of FDA | Response re: statistical language question in FDA Executive Summary |
| 8 October 2009 | E-mail from N. Patel of FDA | Final Panel Pack from FDA |

| Date | Item | Notes |
|---|---|---|
| 8 October 2009 | E-mail from N. Patel of FDA | Notification of Panel Pack shipment |
| 8 October 2009 | E-mail to N. Patel of FDA | Request for final version of Panel Pack and Questions by e-mail |
| 9 October 2009 | E-mail from J. Chen of OSB | Request for clarification about statistical hypotheses in FDA Panel Questions |
| 9 October 2009 | E-mail to N. Patel of FDA | Revision to response to FDA Question #3 |
| 9 October 2009 | P080032/A008 receipt letter | A008 is the hospitalization data correction letter |
| 16 October 2009 | E-mail from J. Chen of OSB | Request for clarification about statistical hypotheses in FDA Panel Questions |
| 16 October 2009 | E-mail to N. Patel of FDA | Request for revised FDA Questions |
| 16 October 2009 | E-mail from N. Patel of FDA | Release date of FDA Questions, redactions, slide exchange |
| 19 October 2009 | E-mail to J. Chen of OSB | Response to questions re: Post-Marketing Registry |
| 19 October 2009 | E-mail to N. Patel of FDA | Copy of response to J. Chen |
| 19 October 2009 | E-mail to N. Patel of FDA | Response re: redactions and slide exchange |
| 20 October 2009 | E-mail to N. Patel of FDA | Afternoon time to respond to questions, slide exchange |
| 20 October 2009 | E-mail from N. Patel of FDA | Response re: afternoon questions, slide exchange |
| 20 October 2009 | E-mail from M. Ryan of FDA | Request for teleconference |
| 21 October 2009 | E-mail to M. Ryan of FDA | Agreement to teleconference |
| 21 October 2009 | E-mail from M. Ryan of FDA | Teleconference information |
| 21 October 2009 | E-mail from M. Ryan of FDA | Correction of teleconference time |
| 22 October 2009 | E-mail from M. Ryan of FDA | Call-in information for 10/23 teleconference |
| 22 October 2009 | E-mail to M. Ryan of FDA | Thanks for call-in information |

| Date | Item | Notes |
|---|---|---|
| 22 October 2009 | E-mail to N. Patel of FDA | Request to provide presenter biographies |
| 27 October 2009 | E-mail to N. Patel of FDA | Question re: 10/29 date on FDA website |
| 27 October 2009 | E-mail from N. Patel of FDA | Response re: 10/29 date (it was an error), slide exchange, copies |
| 27 October 2009 | E-mail to N. Patel of FDA | Request for panel roster |
| 27 October 2009 | E-mail from N. Patel of FDA | Panel roster available 10/28 |
| 27 October 2009 | E-mail to N. Patel of FDA | Thanks for roster response |
| 27 October 2009 | E-mail from N. Patel of FDA | Slides available for exchange |
| 27 October 2009 | E-mail to N. Patel of FDA | Slides incoming |
| 27 October 2009 | E-mail to N. Patel of FDA | Asthmatx slides |
| 27 October 2009 | E-mail from N. Patel of FDA | FDA slides |
| 27 October 2009 | E-mail to N. Patel of FDA | Response re: time frame for slides |
| 27 October 2009 | E-mail to N. Patel of FDA | FDA slide #58 mistake |
| 27 October 2009 | E-mail to N. Patel of FDA | Reminder re: FDA slide #58 mistake |
| 27 October 2009 | E-mail from M. Ryan of FDA | Response re: slide #58 |
| 9 November 2009 | E-mail to M. Ryan of FDA | Outstanding items for approval |
| 9 November 2009 | E-mail from J. Chen of OSB | Response re: PAS protocol timing |
| 9 November 2009 | E-mail from M. Ryan of FDA | Response re: Outstanding items for approval |
| 10 November 2009 | Calls with M. Ryan of FDA and J. Chen of OSB | Outstanding items and schedule for approval |
| 11 November 2009 | E-mail to M. Ryan of FDA | Information for 11/12 call |
| 11 November 2009 | E-mail to M. Ryan of FDA | IFU and Operator's Manual drafts |
| 11 November 2009 | E-mail from M. Ryan of FDA | Request for information on RFC design change, call time change |
| 12 November 2009 | E-mail to M. Ryan of FDA | Response re: RFC design change and call time |
| 12 November 2009 | E-mail to M. Ryan of FDA | RFC design change information |

| Date | Item | Notes |
|---|---|---|
| 12 November 2009 | E-mail to J. Chen of OSB and D. Shure | PAS outlines |
| 12 November 2009 | Call with M. Ryan of FDA | RFC design change, symbols labeling, shelf-life, other topics |
| 12 November 2009 | E-mail to M. Ryan of FDA | High radiation dose compatibility report |
| 12 November 2009 | E-mail to M. Ryan of FDA | Symbols labeling |
| 12 November 2009 | E-mail from M. Ryan of FDA | Catheter symbols OK, question re: RF Controller symbols |
| 12 November 2009 | E-mail to M. Ryan of FDA | Response re: RF Controller symbols |
| 12 November 2009 | E-mail from M. Ryan of FDA | Confirmation that RF Controller symbols are OK |
| 12 November 2009 | E-mail from J. Chen of OSB | Confirmation of call time, participants, dialing info |
| 12 November 2009 | E-mail to J. Chen of OSB | Confirmation of call time, participants |
| 12 November 2009 | E-mail from J. Chen of FDA | Thank-you |
| 16 November 2009 | E-mail to M. Ryan of FDA | Revised SSED |
| 16 November 2009 | E-mail to M. Ryan of FDA | Revised IFU and Operator's Manual and redlines |
| 18 November 2009 | E-mail to J. Chen of OSB | Revised PAS outlines |
| 18 November 2009 | E-mail from M. Ryan of FDA | Request for original Q0044 test results |
| 18 November 2009 | E-mail to M. Ryan of FDA | Summary table of QT-00481 results |
| 18 November 2009 | Call with M. Ryan of FDA | Timeline, outstanding and resolved items |
| 19 November 2009 | E-mail from M. Ryan of FDA | Request for original QT-00481 report |
| 19 November 2009 | E-mail to M. Ryan of FDA | Annotated Module 1 Attachment 6C (QT-00481) |
| 19 November 2009 | E-mail to M. Ryan of FDA | Request for IFU discussion |
| 19 November 2009 | E-mail to M. Ryan of FDA | Schedule through 12/14 |

| Date | Item | Notes |
|---|---|---|
| 20 November 2009 | E-mail from J. Chen of OSB | Request for PAS outline redlines, FDA attendees of 11/13 call |
| 20 November 2009 | E-mail to J. Chen of OSB | PAS outline redlines |
| 23 November 2009 | E-mail from J. Chen of OSB | Thanks for redlines |
| 23 November 2009 | E-mail to J. Chen of OSB | 11/13 call minutes |
| 24 November 2009 | E-mail from J. Chen of OSB | Thanks for minutes, PAS outline comments by 11/24. |
| 24 November 2009 | Call with M. Ryan of FDA | PMA review status (IFU, PAS, testing, shelf life) |
| 24 November 2009 | E-mail from M. Ryan of FDA | Labeling questions |
| 25 November 2009 | E-mail from J. Chen of OSB | Comments on PAS outlines |
| 25 November 2009 | Call with M. Ryan of FDA | IFU comments |
| 30 November 2009 | E-mail to M. Ryan of FDA | IFU and Operator's Manual revisions |
| 1 December 2009 | E-mail to M. Ryan of FDA | Updated SSED |
| 1 December 2009 | E-mail to J. Chen of FDA | Updated PAS outlines |
| 2 December 2009 | E-mail from J. Chen of FDA | Thanks for updated PAS outlines |
| 2 December 2009 | E-mail to M. Ryan of FDA | Request for call about status |
| 2 December 2009 | E-mail to M. Ryan of FDA | Minor corrections to IFU, Ops Manual, and SSED |
| 2 December 2009 | E-mail from M. Ryan of FDA | Status update (no news) |
| 3 December 2009 | E-mail to M. Ryan of FDA | Outstanding items for final approval by 12/14 |
| 3 December 2009 | Call with J. Chen of OSB | Sample size calculation |
| 4 December 2009 | E-mail from M. Ryan of FDA | IFU change requests |
| 4 December 2009 | E-mail to M. Ryan of FDA | Plan for response to IFU change requests |
| 4 December 2009 | E-mail to M. Ryan of FDA | Revisions to IFU |
| 4 December 2009 | E-mail from M. Ryan of FDA | Request for hard copies of amendments to Document Mail Center |

| Date | Item | Notes |
|---|---|---|
| 4 December 2009 | E-mail to M. Ryan of FDA | Response re: sending PMA amendments |
| 7 December 2009 | E-mail to J. Chen of OSB | Revised PAS2 outlines, response re: PAS2 sample size |
| 8 December 2009 | E-mail from J. Chen of OSB | Thanks for revisions and response |
| 8 December 2009 | E-mail to M. Ryan of FDA | Revised SSED |
| 8 December 2009 | E-mail from J. Chen of OSB | Revision to success criteria and dealing with missing data |
| 8 December 2009 | E-mail to M. Ryan of FDA | Revised SSED preclinical section, error corrected |
| 8 December 2009 | E-mail to J. Chen of FDA | Revisions to PAS1 outline, question re: PAS2 |
| 8 December 2009 | E-mail from J. Chen of FDA | Clarification on question |
| 8 December 2009 | E-mail to J. Chen of FDA | Revisions to PAS2 outline |
| 9 December 2009 | E-mail to J. Chen of FDA | Statistician availability |
| 9 December 2009 | E-mail from J. Chen of OSB | Update on PAS2 review |
| 10 December 2009 | Amendment A009 | Hard copies of high dose compatibility report |
| 10 December 2009 | E-mail to M. Ryan of FDA | Revised SSED |
| 10 December 2009 | E-mail to J. Chen of FDA | Revisions to PAS1 and PAS2 outlines |
| 10 December 2009 | E-mail to M. Ryan of FDA | Revised Operator's Manual |
| 10 December 2009 | E-mail to M. Ryan of FDA | Availability 12/11 |
| 11 December 2009 | Amendment A010 | Final catheter package labels |
| 11 December 2009 | A009 receipt letter | High dose compatibility report |
| 14 December 2009 | A010 receipt letter | Final catheter package labels |
| 14 December 2009 | E-mail from M. Ryan of FDA | Update on PMA review (looking at labeling) |
| 17 December 2009 | E-mail from M. Ryan of FDA | Redlined IFU |
| 17 December 2009 | E-mail to M. Ryan of FDA | Revised IFU incorporating FDA changes |

| Date | Item | Notes |
|---|---|---|
| 17 December 2009 | E-mail from M. Ryan of FDA | Request for revised Ops Manual |
| 18 December 2009 | E-mail from M. Ryan of FDA | Two issues re: IFU |
| 18 December 2009 | E-mail to M. Ryan of FDA | Revised IFU incoming |
| 18 December 2009 | E-mail to M. Ryan of FDA | Confirming removal of potential risk language |
| 18 December 2009 | E-mail to M. Ryan of FDA | Revised IFU and Ops Manual |
| 18 December 2009 | E-mail to M. Ryan of FDA | Revised SSED |
| 21 December 2009 | E-mail to L. Schultheis of FDA | Efforts toward approval by year-end |
| 22 December 2009 | E-mail from L. Schultheis of FDA | Response re: year-end approval efforts |
| 22 December 2009 | PMA inspection letter | Voluntary action indicated (VAI) |
| 23 December 2009 | E-mail to J. Salyer and M. Choe of FDA | Response to PMA inspection letter |
| 24 December 2009 | E-mail from M. Choe of FDA | PAS conditions form |
| 27 December 2009 | E-mail to M. Choe of FDA | Completed and signed PAS conditions form |
| 4 January 2010 | E-mail to M. Ryan of FDA | Inspection question answered |
| 22 January 2010 | E-mail from M. Ryan of FDA | Request for patient labeling |
| 22 January 2010 | E-mail from J. Chen of FDA | Recommendation to work on PAS protocols |
| 24 January 2010 | E-mail to M. Ryan of FDA | Patient brochure and guidance checklist |
| 27 January 2010 | E-mail to J. Chen of FDA | Response re: timing of PAS protocols |
| 1 February 2010 | E-mail from J. Chen of FDA | Response re: timing of PAS protocols |
| 4 February 2010 | E-mail to M. Ryan of FDA | Request for update on patient brochure review |
| 5 February 2010 | E-mail from M. Ryan of FDA | Update on patient brochure review (no news) |

| Date | Item | Notes |
|---|---|---|
| 7 February 2010 | E-mail to J. Chen of FDA | PAS #2 protocol |
| 15 February 2010 | Email to M. Ryan of FDA | Request for quicker review of patient brochure |
| 16 February 2010 | E-mail to L. Schultheis | Request for quicker review of patient brochure |
| 16 February 2010 | E-mail from J. Chen of FDA | Thanks for PAS #2 protocol |
| 17 February 2010 | E-mail to J. Chen of FDA | PAS #1 protocol (AIR2x) |
| 23 February 2010 | E-mail from M. Ryan of FDA | Comments on patient brochure |
| 24 February 2010 | E-mail to M. Ryan of FDA | Request for interactive review of patient brochure |
| 24 February 2010 | E-mail to M. Ryan of FDA | Revised patient brochure |
| 26 February 2010 | E-mail to M. Ryan of FDA | Minor revisions to patient brochure |
| 2 March 2010 | E-mail from J. Chen of FDA | Notice that protocol comments may not come until April |
| 5 March 2010 | E-mail to M. Ryan of FDA | Revised patient brochure, validation, drug examples |
| 5 March 2010 | E-mail from M. Ryan of FDA | Unable to review before morning call |
| 5 March 2010 | Conference call with FDA | Patient brochure review |
| 7 March 2010 | E-mail to M. Ryan of FDA | Patient brochure Rev 14 |
| 9 March 2010 | E-mail from M. Ryan of FDA | Suggested re-write of patient brochure |
| 9 March 2010 | E-mail to M. Ryan of FDA | Patient brochure Rev 16 |
| 17 March 2010 | E-mail from M. Ryan of FDA | Patient brochure revisions |
| 17 March 2010 | E-mail to M. Ryan of FDA | Patient Brochure 3/17 rev |
| 19 March 2010 | E-mail to M. Ryan of FDA | Request for brochure review status |
| 19 March 2010 | E-mail from L. Schultheis of FDA | Will try to provide feedback early next week |
| 19 March 2010 | E-mail to DB Tillman of FDA | Background on our review and request for call |
| 22 March 2010 | E-mail to M. Ryan of FDA | Request for call on status |

| Date | Item | Notes |
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| 22 March 2010 | E-mail from DB Tillman of FDA | No call necessary, clinical deputy Dr. Markham Luke will continue involvement in review after DBT departure |
| 22 March 2010 | E-mail to DB Tillman of FDA | Thanks for reply |
| 23 March 2010 | Conversation with M. Ryan of FDA | Status of brochure and PMA review |
| 23 March 2010 | E-mail to M. Ryan of FDA | Checking on redlined brochure |
| 24 March 2010 | E-mail from M. Ryan of FDA | Typos in IFU |
| 24 March 2010 | E-mail to M. Ryan of FDA | Corrected IFU |
| 24 March 2010 | E-mail from M. Ryan of FDA | Effect of IFU dyspepsia correction on brochure |
| 24 March 2010 | E-mail to M. Ryan of FDA | No effect on brochure from IFU dyspepsia correction |
| 25 March 2010 | E-mail from M. Ryan of FDA | Good changes in IFU, request for the same in Ops Manual |
| 25 March 2010 | E-mail to M. Ryan of FDA | Confirmation of Ops Manual changes, and SSED too |
| 25 March 2010 | E-mail to M. Ryan of FDA | Revised Ops Manual and SSED |
| 25 March 2010 | E-mail from M. Ryan of FDA | Thanks for revisions |
| 30 March 2010 | Call with M. Ryan of FDA | Status update (still with PMA staff) |
| 1 April 2010 | Call with L. Byrd of FDA | Status update |
| 8 April 2010 | Call with L. Fisher of FDA | Status update |
| 8 April 2010 | E-mail to L. Fisher of FDA | Status update and contact info during Debbie's vacation |
| 9 April 2010 | E-mail from M. Ryan of FDA | Changes to labeling |
| 10 April 2010 | E-mail to M. Ryan of FDA | IFU, Ops Manual, and brochure revisions |
| 13 April 2010 | E-mail from M. Ryan of FDA | Minor brochure revisions |
| 13 April 2010 | E-mail to M. Ryan of FDA | Revised brochure |
| 14 April 2010 | E-mail from M. Ryan of FDA | Thanks for revised brochure |

| Date | Item | Notes |
|---|---|---|
| 16 April 2010 | E-mail from J. Chen of FDA | Feedback on PAS protocols |
| 19 April 2010 | E-mail to M. Ryan of FDA | Revised SSED |
| 19 April 2010 | E-mail from M. Ryan of FDA | Request for preclinical AE info for SSED |
| 20 April 2010 | E-mail to M. Ryan of FDA | Commitment to provide AE info by morning |
| 20 April 2010 | E-mail to M. Ryan of FDA | Revised SSED with AE info |
| 21 April 2010 | E-mail from M. Ryan of FDA | Thanks for updated SSED |
| 27 April 2010 | Approval Order | |
| 29 April 2010 | Amendment A011 | Final approved labeling |